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REVIEW ARTICLE

Molecular Pathogenesis and a Consequent Classification of Multiple Myeloma

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ABSTRACT

There appear to be two pathways involved in the pathogenesis of premalignant non-immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM). Nearly half of tumors are nonhyperdiploid, and mostly have one of five recurrent IgH translocations: 16% *11q13* (*CCN D1*), 3% *6p21* (*CCN D3*), 5% *16q23* (*MAF*), 2% 20q12 (*MAFB*), and 15% *4p16* (*FGFR3* and *MMSET*). The remaining hyperdiploid tumors have multiple trisomies involving chromosomes 3, 5, 7, 9, 11, 15, 19, and 21, and infrequently one of these five translocations. Although cyclin D1 is not expressed by healthy lymphoid cells, it is bi-allelically dysregulated in a majority of hyperdiploid tumors. Virtually all MM and MGUS tumors have dysregulated and/or increased expression of cyclin D1, D2, or D3, providing an apparent early, unifying event in pathogenesis. The patterns of translocations and cyclin D expression (TC) define a novel classification that includes eight groups: 11q; 6p; MAF; 4p; D1 (34%); D1+D2 (6%); D2 (17%); and none (2%). The hyperdiploid D1 group is virtually absent in extramedullary MM and MM cell lines, suggesting a particularly strong dependence on interaction with the bone marrow microenvironment. Despite shared progression events (*RAS* mutations, *MYC* dysregulation, p53 mutations, and additional disruption of the retinoblastoma pathway), the phenotypes of MGUS and MM tumors in the eight TC groups is determined mainly by early oncogenic events. Similar to acute lymphocytic leukemia, MM seems to include several diseases (groups) that have differences in early or initiating events, global gene expression patterns, bone marrow dependence, clinical features, prognosis, and response to therapy.

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INTRODUCTION

Multiple myeloma (MM), presently an incurable plasma cell (PC) malignancy with a yearly incidence of 14,000 in the United States and a median survival of 3 years, accounts for approximately 20% of deaths from hematologic malignancy and nearly 2% of deaths from cancer.[1] Often it is preceded by a premalignant tumor called monoclonal gammopathy of undetermined significance (MGUS), which occurs in about 3% of individuals over the age of 50.[2] The prevalence of both MGUS and MM increases markedly with age, and is about two-fold higher in African Americans than in whites.[3] Despite evidence for some clustering of MM and MGUS within families, the roles of genetic background and environment remain unclear.[4,5]

MM Is a Plasmablast/Plasma-Cell Tumor of Post–Germinal Center B Cells

Most B-cell tumors, including MM, involve germinal center (GC) or post-GC B cells that have modified their immunoglobulin (*Ig*) genes by sequential rounds of somatic hypermutation and antigen selection, and sometimes by IgH switch recombination. These two B cell–specific DNA modification processes, which occur mainly in GC B cells, sometimes can cause mutations or double-strand DNA breaks in or near non-*Ig* genes, including oncogenes.[6] Post-GC B cells can generate plasmablasts

(PBs) that have successfully completed somatic hypermutation, antigen selection, and IgH switching before migrating to the bone marrow (BM), where stromal cells enable terminal differentiation into long-lived PCs.[7] Although PCs can be generated from pre-GC B cells, MM and non-IgM MGUS are exclusively post-GC tumors that have phenotypic features of PBs/long-lived PCs, and usually are distributed at multiple sites in the BM. A critical feature shared by MGUS and MM is an extremely low rate of proliferation, usually with no more than a small percentage of cycling cells until late stages of MM.[8] There appear to be two kinds of cell populations in non-IgM MGUS or MM tumors. A small fraction of proliferative tumor cells have a phenotype that is similar to a PB or a pre-PB that might express some B-cell markers (CD19, CD20, CD45) but not some PC markers (CD138), although the precise phenotype(s) and location(s) of the proliferating tumor cell remains a contentious issue.[9,10] However, most of the tumor cells are nonproliferative; although perhaps not fully differentiated, these cells have a phenotype that is similar to healthy, terminally differentiated, long-lived BM PCs. It is unclear if this second cell population retains the ability to revert to a proliferative phenotype. In any case, the occurrence of these two kinds of tumor cells is an important consideration in the design and evaluation of therapies.

Stages of MM

A clonal PC neoplasm must expand to approximately 10^9 cells before it produces enough Ig to be recognized as a monoclonal Ig (M-Ig) by serum electrophoresis. For MGUS, the M-Ig is 0.5 to 3g/dl, and the tumor cells comprise no more than 10% of the mononuclear-cells in the BM (Fig 1). Depending on the level of M-Ig, 0.6% to 3% per year of patients with non-IgM MGUS progress to MM expressing the same M-Ig.[11] There are no unequivocal genetic or phenotypic markers that distinguish MGUS from MM tumor cells, so that it is not possible to predict if and when an MGUS tumor will progress to MM. Also, it remains unclear to what extent intrinsic genetic or epigenetic changes in the MGUS tumor cell versus extrinsic changes in non-tumor cells affect progression. Primary amyloidosis is caused by an MGUS tumor (sometimes with such a small number of tumor cells that M-Ig is not detected by serum electrophoresis) that is symptomatic because of pathologic deposits of portions of the M-Ig in critical tissues.[12] MM is distinguished from MGUS by having a BM tumor content $>$ 10%.[13] Smoldering MM, which has a stable BM tumor content of $>$ 10%, but no osteolytic lesions or other complications of malignant MM, has a high probability of rapidly progressing to frankly malignant MM with osteolytic lesions and/or an increasing tumor mass. Further progression of MM is associated with increasingly severe secondary features (lytic bone lesions, anemia, immunodeficiency, renal impairment), and in some patients the occurrence of tumor in extramedullary locations. Extramedullary MM is a more aggressive tumor that often is called secondary or primary plasma cell leukemia (PCL), depending on whether or not preceding intramedullary myeloma has been recognized. Human MM cell lines (HMCL) sometimes can be generated, but usually only from extramedullary tumors.

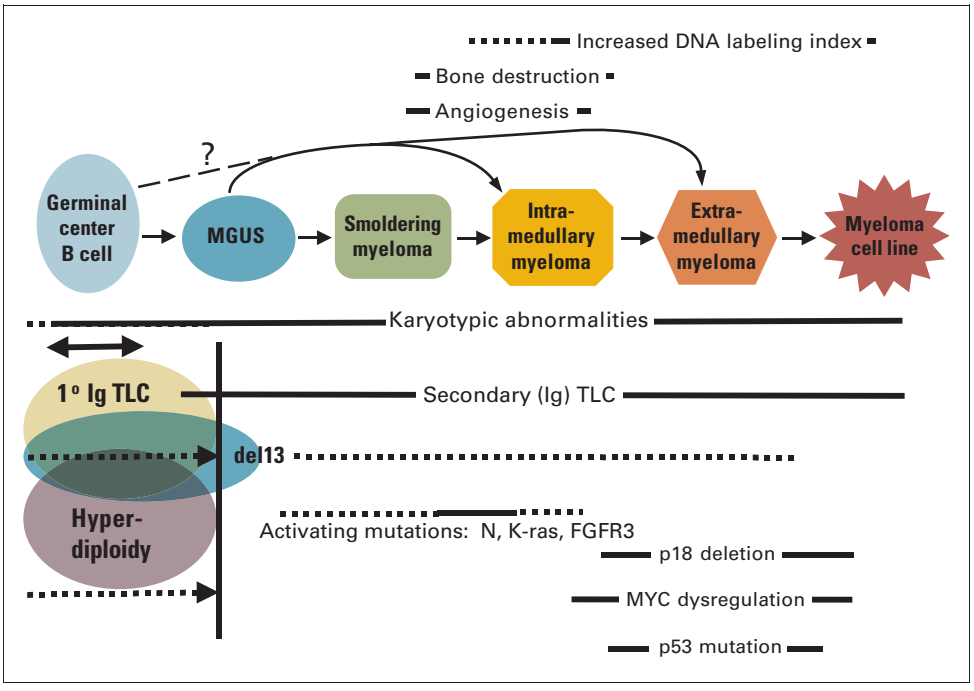

Fig 1. Disease stages and timing of oncogenic events. The earliest oncogenic changes are present in monoclonal gammopathy of undetermined significance (MGUS), and involve two minimally overlapping pathways (ovals), both of which substantially overlap the del 13 pathway (striped oval). Primary immunoglobulin (Ig) translocations (TLC) are thought to occur in germinal center B cells (bi-directional arrow) but the timing for the other two pathways (dashed arrows) is unclear. Other karyotypic abnormalities, including secondary (Ig) TLC may occur at all stages. Activating mutations of K- or N-RAS appear to mark, if not cause, the MGUS to multiple myeloma (MM) transition in some cases, but sometimes occur during subsequent progression of MM. Late oncogenic events that occur at a time when tumors are becoming more aggressive include MYC dysregulation by secondary (Ig) TLC, bi-allelic deletion of p18, and loss or mutation of p53.

Ig Translocations Are Present in a Majority of MM Tumors

Many B-cell tumors, including MM, have chromosomal translocations that are mediated by errors in VDJ recombination or one of the other two B cell specific DNA modification mechanisms. The consequence of these translocations is dysregulation or increased expression of an oncogene that is positioned near a strong Ig enhancer. The prevalence of IgH translocations varies somewhat with the disease stage: nearly 50% in MGUS or SMM, 55% to 73% in intramedullary MM, 85% in primary PCL, and > 90% in HMCL.[14-16] There are five recurrent chromosomal partners (oncogenes) that are involved in IgH translocations in MGUS and MM: *4p16* (*MMSET* and usually *FGFR3*), *6p21* (*CCN D3*), *11q13* (*CCN D1*), *16q23* (*c-MAF*), and *20q11* (*MAFB*).[17-22] Together, the combined prevalence of these five IgH translocation partners is about 40% in MM, with approximately 15% *4p16*, 3% *6p21*, 15% *11q13*, 5% *16q23*, and 2% *20q11*. The apparent markedly decreased prevalence of IgH translocations involving *4p16* and *16q23* in MGUS suggests that these translocations can cause de novo MM and/or are associated with rapid progression from MGUS to MM. The mostly simple reciprocal translocations involving the five recurrent translocation partners appear to be primary translocations that usually are mediated by errors in IgH switch recombination during the maturation of B cells in germinal centers.[23]

About 3% of MM tumors have secondary IgH translocations that target c-*myc* at 8q24. Secondary translocations that dysregulate an *MYC* gene (c- ≫ N- > L-) by juxtaposing it to an Ig locus (IgH ~ Igλ ≫ Igκ) or to one of many other poorly characterized chromosomal loci are late progression events.[16,22,24] The *MYC* translocations are absent or rare in MGUS but occur in 15% of MM tumors, 45% of advanced tumors, and 90% of HMCL. These translocations are not mediated by the B cell–specific DNA modification mechanisms, which are inactive in healthy or tumor PCs. In contrast to the primary translocations described above, these secondary events often include unbalanced and complex translocations and insertions that can involve three chromosomes, sometimes with associated amplification, duplication, inversion, or deletion.

Other IgH translocation partners have been identified in about 15% of MM tumors, and in more than 25% of MGUS tumors.[14,15,22,25] The other translocation partners, which are poorly characterized, appear to be mostly nonrecurrent or rare. These translocations seem to share the structural complexity and lack of IgH switch region involvement observed for MYC translocations, suggesting that they may represent secondary translocations, which can occur at any time during tumor progression, including MGUS (A. Gabrea, unpublished data).[23] Translocations involving an Igλ locus occur in approximately 10% of MGUS tumors, and approximately 20% of advanced MM tumors or HMCL.[22,25] Translocations involving an Igκ locus are rare, occurring in only a small percentage of MM tumors. Nearly half of IgL translocations in advanced MM tumors or HMCL target an *MYC* gene. Significantly, although all HMCL analyzed have either an IgH or IgL translocation, approximately 30% of MM tumors and 45% of MGUS tumors do not have either an IgH or IgL translocation. Surprisingly, however, two independent Ig translocations are found in 5% of MGUS tumors, 25% of advanced MM tumors, and 58% of HMCL, consistent with an accumulation of secondary Ig translocations during tumor progression (A. Gabrea, unpublished data).[24]

Hyperdiploid and Nonhyperdiploid Tumors

All MGUS and MM tumors have numeric and/or structural chromosome abnormalities.[22] Although no gene has yet been identified, loss of chromosome13/13q/13q14 sequences, which occurs in approximately 60% of MM tumors and nearly 50% of MGUS tumors, was one of the first chromosomal abnormalities associated with a poor prognosis.[26,27] Nearly half of MM tumors are hyperdiploid (HRD; 48-75 chromosomes), and often have multiple trisomies involving eight odd chromosomes (3,5,7,9,11,15,19,21). Nonhyperdiploid (NHRD) tumors (< 48 or > 75 chromosomes), which can be hypodiploid, pseudodiploid or subtetraploid, were noted to have a poorer prognosis than HRD tumors.[28] More recently it was reported that at least three of the five recurrent IgH translocations occur predominantly in NHRD tumors.[29,30] Secondary translocations, which appear to include all MYC translocations, most—if not all—IgL translocations, most IgH translocations not involving the five recurrent partners, and some IgH translocations involving the five recurrent partners, seem to occur with a similar prevalence in HRD and NHRD tumors. Loss of chromosome 13 sequences occurs in 72% of NHRD tumors but only 37% of HRD tumors. It remains to be clarified if ploidy and loss of chromosome 13 sequences are independent prognostic factors.

Dysregulation of cyclin D1, -2, or -3: A Unifying, Early Oncogenic Event in MM and MGUS

Most tumor cells in MGUS and MM appear more similar to healthy, nonproliferating PCs than to healthy, but highly proliferating PBs, for which 30% or more of the cells can be in S phase. Surprisingly, however, despite a very low proliferation index, the level of cyclin D1, cyclin D2, or cyclin D3 mRNA in virtually all MM and MGUS tumors is relatively high, comparable with the level of *cyclin D2* mRNA expressed in healthy proliferating PBs, and distinctly higher than in healthy BM PCs.[31] Approximately 25% of MGUS or MM tumors have an IgH translocation that directly dysregulates *CCN D1* (*11q13*), *CCN D3* (*6p21*), or a *MAF* gene (*MAF*, *16q23* or *MAFB*, *20q11*) encoding a transcription factor that targets cyclin D2

(Fig 2). Nearly 40% of MGUS and MM tumors do not have a t(11;14), but are HRD and bi-allelically express cyclin D1, whereas healthy BM PCs generally do not express detectable cyclin D1. Most other tumors, including those with a t(4;14), have increased expression of cyclin D2 compared with healthy BM PCs.

Model for the Molecular Pathogenesis of MGUS and MM

It has been proposed that there are two pathways of pathogenesis: an NHRD pathway that usually includes one of the five recurrent IgH translocations as an early event, and an HRD pathway that is associated with multiple trisomies of eight odd chromosomes but is mediated by a yet-to-be-determined mechanism.[22,29,31] As summarized in the preceding section, dysregulation of a *cyclin D* gene—sometimes as a consequence of a primary IgH translocation but otherwise by presently unknown mechanisms—appears to be a unifying and early event. The dysregulation of a *cyclin D* gene may render the cells more susceptible to proliferative stimuli, resulting in selective expansion as a result of interaction with BM stromal cells that produce interleukin-6, insulin-like growth factor 1, and other cytokines. Loss of chromosome 13/13q sequences also seems to be an early event shared by MGUS and MM tumors. Unfortunately, we do not yet understand the relative timing of primary IgH translocations, aneuploidy (including multiple trisomies and loss of chromosome 13 sequences), and cyclin D dysregulation. Secondary chromosome translocations and other karyotypic abnormalities can occur at all stages of tumorigenesis. Mutually exclusive activating mutations of *K-* or *N-RAS* (or *FGFR3* when there is a t(4;14) translocation) are rare in MGUS, but the prevalence of *RAS* mutations is 30% to 40% in early MM and slightly higher in advanced MM; *FGFR3* mutations may occur more frequently in advanced MM.[32] Secondary *MYC* translocations are late progression events that may occur as a tumor becomes less dependent on BM stromal cells and/or more proliferative. Despite alteration of the RB pathway by dysregulation of a *cyclin D* gene in virtually all MGUS and MM tumors, inactivation of an additional component of this pathway (*p18INK4c* or retinoblastoma) can be a late-progression event that is associated with enhanced proliferation. Mutations and/or mono-allelic deletion of *p53* also appear to be late-progression events. The timing of other events, such as *PTEN* mutations, is unknown.[22]

*Translocation/*cyclin D *Expression Classification Based on Early Pathogenic Events*

On the basis, in large part, of the hypotheses presented in the preceding paragraphs, a supervised analysis of gene expression profiles provides the basis for a molecular classification of MM.[31] In addition to determining the expression level of *cyclin D1*, *-2*, and *-3*, gene expression profiling can effectively identify MM tumors that overexpress the oncogenes dysregulated by the five recurrent IgH translocations: *11q13* (*CCN D1*); *6p21* (*CCN D3*); *4p16* (*MMSET* and usually *FGFR3*); *16q23* (*maf*); and *20q11* (*mafB*). These groups (Table 1) can be distinguished on the basis of the Ig translocation present, and *cyclin D* expression: *11q13* (16%) and *6p21* tumors (3%) express high levels of either *cyclin D1* or *cyclin D3* as a result of an *Ig* translocation; *D1* tumors (34%) ectopically express low to moderate levels of *cyclin D1* despite the absence of

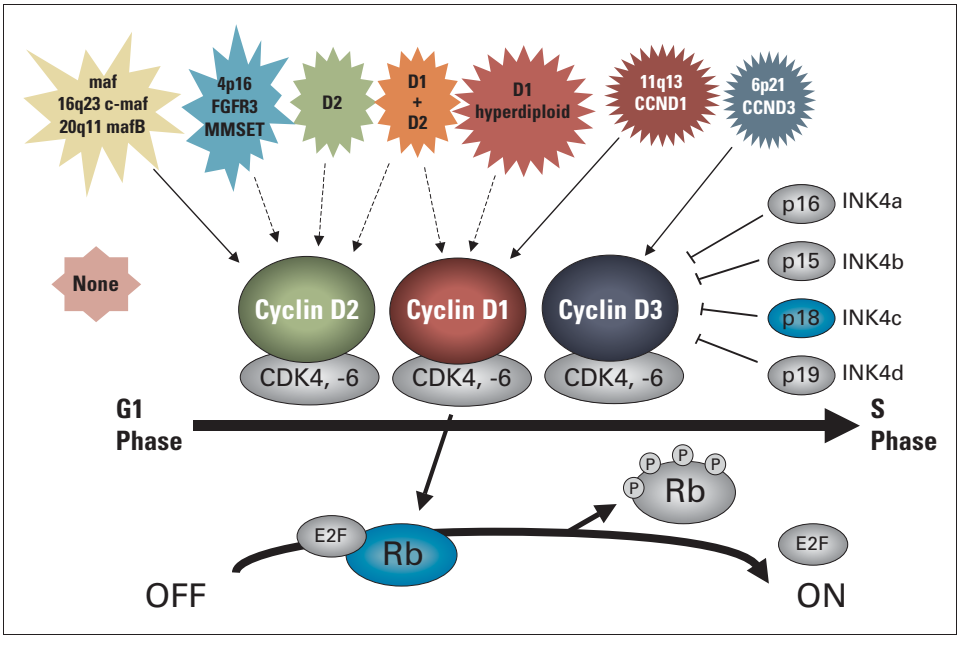

Fig 2. Alteration of Rb pathway by both early and late pathogenic events. An early pathogenic event in tumors from seven of the translocations and cyclin D expression (TC) groups is dysregulation of one of the three *cyclin D* genes, either as a consequence of an *Ig* translocations (TLC; solid arrow), or by an unknown mechanism (dashed arrow). Increased expression of one of the cyclin D proteins facilitates activation of CDK4 (or CDK6), which then phosphorylates and inactivates Rb so that E2F can facilitate G1 > S cell cycle progression. This reaction is regulated by CDK inhibitors (INK4a-d), so that increased proliferation of some MM tumors occurs only after a late oncogenic event that inactivates Rb or p18INK4c.

Table 1. Translocation and *cyclin D* Groups

Group	Primary Translocation	Gene at Breakpoint	D-Cyclin	Ploidy	Proliferation Index	Bone disease (% MRI Pos)	Frequency (%)	Prognosis
6p21	*6p21*	*CCND3*	D3	NH	Average	100	3	? Good
11q13	*11q13*	*CCND1*	D1	D, NH	Average	94	16	Good
D1	None	None	D1	H	Low	86	34	Good
D1+D2	None	None	D1 and D2	H	High	100	6	? Poor
D2	None	None	D2	H, NH	Average	67	17	?
None	None	None	None	NH	Average	100	2	? Good
4p16	*4p16*	*FGFR3/MMSET*	D2	NH > H	Average	57	15	Poor
maf	*16q23*	*c-maf*	D2	NH	High	55	5	Poor
	20q11	*mafB*					2	

Abbreviations: MRI, magnetic resonance imaging; pos, positive; D, diploid; H, hyperdiploid; NH, nonhyperdiploid.

a t(11;14) translocation; *D1+D2* (6%) in addition express *cyclin D2*. *D2* tumors (17%) are a mixture of tumors that do not fall into one of the other groups, and express *cyclin D2*; None (1%) express no D-type cyclins. *4p16* tumors (15%) express high levels of *cyclin D2*, and also *MMSET* (and in most cases *FGFR3*) as a result of a t(4;14) translocation; *maf* tumors (7%) express the highest levels of *cyclin D2*, and also high levels of either *c-maf* or *mafB*, consistent with the possibility that both *maf* transcription factors upregulate the expression of *cyclin D2*. Supervised hierarchical cluster analysis of gene expression profiles demonstrates that the translocation/*cyclin D* expression (TC) classification identifies homogeneous groups of tumors with distinctive patterns of gene expression, and by corollary, phenotype. Although not unequivocally established, we think that the basis for assignment of tumors to the TC groups is focused primarily on very early if not initiating oncogenic events that are shared by MGUS and MM tumors, although the *D1+D2* group might represent an exception.

Implications of the TC Classification of MGUS and MM

In addition to having shared gene expression profiles, we have identified important biologic and clinical correlates associated with the TC groups (Table 1).[31] For example, the TC *D1* group of tumors is absent or underrepresented in PCL and HMCL, suggesting that these tumors have a particularly strong dependence on a continued interaction with bone marrow stromal cells. In addition, we have found that lytic bone disease correlates with the TC classification, with high prevalence (approximately 90%) in TC *6p21*, TC *11q13*, TC *D1* and TC *D1+D2*, and lower prevalence (approximately 55%) in TC *4p16* and TC *maf*. It has also become clear that specific IgH translocations have a profound prognostic significance.[33,34] Patients with tumors that have a t(4;14) translocation (TC *4p16*) have a substantially shortened survival either with standard or high-dose therapy (median overall survival, 26 months and 33 months, respectively), and patients with a t(14;16) (TC *maf*) have a similarly poor if not worse prognosis (median overall survival, 16 months with conventional therapy). By contrast, patients with tumors that have a t(11;14) translocation (TC *11q13*) appear to have a better survival following both conventional chemotherapy and high-dose therapy. Similarly we suspect that the TC *D1* group, representing most of the hyperdiploid patients, shares the good prognosis associated with hyperdiploidy. There are too few patients to draw conclusions about TC *6p21* but given the overlapping gene expression profile with TC *11q13* and obvious mechanistic similarities, it makes sense to group them together. Similarly it makes sense to group the t(14;16) (*c-maf*) with t(14;20) (*mafB*) into the TC *maf* group. Although we do not have mature data at this time we suspect that *D1+D2*, which have a higher proliferative index, and are over-represented in relapsed patients, have a poor prognosis. The TC none group is very small, but because it represents patients with macrofocal disease it would appear to have a good prognosis. These results suggest that the TC classification, which appears to be based on the earliest events in pathogenesis, may be a clinically useful way to classify patients into groups that have distinct subtypes of MM (and MGUS) tumors.[33,35-37] One might argue that some or all of the TC groups represent different disease that may require different therapeutic approaches. However, it is likely that a definitive molecular classification will require modification as additional initiating and progression events are identified. In fact, it seems unlikely there will be a single classification system, but instead the classification of MM tumors will depend on the availability and response to an ever-widening variety of therapeutic regiments. Yet the TC groups that are based on what appear to be early, or initiating, pathogenic events should continue to provide a foundation for clinically relevant insights.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

1. Ries LAG, Eisner MP, Kosary CL, et al: SEER Cancer Statistics Review, 1975-2001. Bethesda, MD, National Cancer Institute, 2004

2. Kyle RA, Therneau TM, Rajkumar SV, et al: Prevalence of monoclonal gammopathy of undetermined significance (MGUS) among Olmsted County, MN residents over 50 years of age. Blood 102, 2003 (abstr 3476a)

3. Cohen HJ, Crawford J, Rao MK, et al: Racial differences in the prevalence of monoclonal gammopathy in a community-based sample of the elderly. Am J Med 104:439-444, 1998

4. Lynch HT, Watson P, Tarantolo S, et al: Phenotypic heterogeneity in multiple myeloma families. J Clin Oncol 23:685-693, 2005

5. Lynch HT, Sanger WG, Pirruccello S, et al: Familial multiple myeloma: A family study and review of the literature. J Natl Cancer Inst 93:1479-1483, 2001

6. Pasqualucci L, Neumeister P, Goossens T, et al: Hypermutation of multiple proto-oncogenes in B-cell diffuse large-cell lymphomas. Nature 412:341-346, 2001

7. Kuehl WM, Bergsagel PL: Multiple myeloma: Evolving genetic events and host interactions. Nat Rev Cancer 2:175-187, 2002

8. Rajkumar SV, Fonseca R, Dewald GW, et al: Cytogenetic abnormalities correlate with the plasma cell labeling index and extent of bone marrow involvement in myeloma. Cancer Genet Cytogenet 113:73-77, 1999

9. Matsui W, Huff CA, Wang Q, et al: Characterization of clonogenic multiple myeloma cells. Blood 103:2332-2336, 2004

10. Pilarski LM, Hipperson G, Seeberger K, et al: Myeloma progenitors in the blood of patients with aggressive or minimal disease: Engraftment and self-renewal of primary human myeloma in the bone marrow of NOD SCID mice. Blood 95:1056-1065, 2000

11. Kyle RA, Therneau TM, Rajkumar SV, et al: A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 346:564-569, 2002

12. Hayman SR, Bailey RJ, Jalal SM, et al: Translocations involving the immunoglobulin heavy-chain locus are possible early genetic events in patients with primary systemic amyloidosis. Blood 98:2266-2268, 2001

13. Malpas JS, Bergsagel DE, Kyle R, et al: Myeloma: Biology and Management (ed 3). Oxford, United Kingdom, Elsevier, 2004

14. Fonseca R, Blood E, Rue M, et al: Clinical and biologic implications of recurrent genomic aberrations in myeloma. Blood 101:4569-4575, 2003

15. Avet-Loiseau H, Facon T, Grosbois B, et al: Oncogenesis of multiple myeloma: 14q32 and 13q chromosomal abnormalities are not randomly distributed, but correlate with natural history, immunological features, and clinical presentation. Blood 99:2185-2191, 2002

16. Shou Y, Martelli ML, Gabrea A, et al: Diverse karyotypic abnormalities of the c-myc locus associated with c-myc dysregulation and tumor progression in multiple myeloma. Proc Natl Acad Sci U S A 97:228-233, 2000

17. Chesi M, Bergsagel PL, Brents LA, et al: Dysregulation of cyclin D1 by translocation into an IgH gamma switch region in two multiple myeloma cell lines. Blood 88:674-681, 1996

18. Chesi M, Bergsagel PL, Shonukan OO, et al: Frequent dysregulation of the c-maf proto-oncogene at 16q23 by translocation to an Ig locus in multiple myeloma. Blood 91:4457-4463, 1998

19. Chesi M, Nardini E, Brents LA, et al: Frequent translocation t(4;14)(p16.3;q32.3) in multiple myeloma is associated with increased expression and activating mutations of fibroblast growth factor receptor 3. Nat Genet 16:260-264, 1997

20. Chesi M, Nardini E, Lim RSC, et al: The t(4;14) translocation in myeloma dysregulates both FGFR3 and a novel gene, MMSET, resulting in IgH/MMSET hybrid transcripts. Blood 92:3025-3034, 1998

21. Shaughnessy J, Gabrea A, Qi Y, et al: Cyclin D3 at 6p21 is dysregulated by recurrent Ig translocations in multiple myeloma. Blood 98:217-223, 2001

22. Kuehl WM, Bergsagel PL: Multiple myeloma: Evolving genetic events and host interactions. Nat Rev Cancer 2:175-187, 2002

23. Bergsagel PL, Kuehl WM: Chromosomal translocations in multiple myeloma. Oncogene 20:5611-5622, 2001

24. Avet-Loiseau H, Gerson F, Margrangeas F, et al: Rearrangements of the c-myc oncogene are present in 15% of primary human multiple myeloma tumors. Blood 98:3082-3086, 2001

25. Fonseca R, Bailey RJ, Ahmann GJ, et al: Genomic abnormalities in monoclonal gammopathy of undetermined significance. Blood 100:1417-1424, 2002

26. Tricot G, Sawyer J, Jagannath S, et al: Poor prognosis in multiple myeloma is associated with partial or complete deletions of chromosome-13 or abnormalities involving 11q and not with other karyotype abnormalities. Exp Hematol 23:867, 1995

27. Fonseca R, Oken MM, Harrington D, et al: Deletions of chromosome 13 in multiple myeloma identified by interphase FISH usually denote large deletions of the q arm or monosomy. Leukemia 15:981-986, 2001

28. Smadja NV, Bastard C, Brigaudeau C, et al: Hypodiploidy is a major prognostic factor in multiple myeloma. Blood 98:2229-2238, 2001

29. Smadja NV, Leroux D, Soulier J, et al: Further cytogenetic characterization of multiple myeloma confirms that 14q32 translocations are a very rare event in hyperdiploid cases. Genes Chromosomes Cancer 38:234-239, 2003

30. Fonseca R, Debes-Marun CS, Picken EB, et al: The recurrent IgH translocations are highly associated with non-hyperdiploid variant multiple myeloma. Blood 102:2562-2567, 2003

31. Bergsagel PL, Kuehl WM, Zhan F, et al: Cyclin D dysregulation: An early and unifying pathogenic event in multiple myeloma. Blood 106:296-303, 2005

32. Chesi M, Brents LA, Ely SA, et al: Activated fibroblast growth factor receptor 3 is an oncogene that contributes to tumor progression in multiple myeloma. Blood 97:729-736, 2001

33. Fonseca R, Blood E, Rue M, et al: Clinical and biologic implications of recurrent genomic aberrations in myeloma. Blood 101:4569-4575, 2003

34. Moreau P, Facon T, Leleu X, et al: Recurrent 14q32 translocations determine the prognosis of multiple myeloma, especially in patients receiving intensive chemotherapy. Blood 100:1579-1583, 2002

35. Garand R, Avet-Loiseau H, Accard F, et al: t(11;14) and t(4;14) translocations correlated with mature lymphoplasmacytoid and immature morphology, respectively, in multiple myeloma. Leukemia 17:2032-2035, 2003

36. Avet-Loiseau H, Garand R, Lode L, et al: Translocation t(11;14)(q13;q32) is the hallmark of IgM, IgE, and nonsecretory multiple myeloma variants. Blood 101:1570-1571, 2003

37. Fonseca R, Blood EA, Oken MM, et al: Myeloma and the t(11;14)(q13;q32): Evidence for a biologically defined unique subset of patients. Blood 99:3735-3741, 2002