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EDITORIAL

An internationally recognized uniform cytogenetic classification system is needed for multiple myeloma

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In this issue of *Leukemia* there are 3 papers[1–3] dealing with the prognostic impact of abnormal cytogenetics in patients with multiple myeloma. Two address whether bortezomib overcomes the poor outcomes associated with deletion 13,[1,2] whereas the final one evaluates the role different fluorescent *in situ* hybridization (FISH) abnormalities play in the prognosis of patients undergoing autologous hematopoietic stem cell transplantation (HSCT).[3]

As background, the reader should be aware of two important concepts and a controversy. The first is the distinction between deletion of chromosome 13 by metaphase cytogenetics (M-Δ13) and by interphase FISH (F-Δ13).[3–6] M-Δ13 is found in only 15% of all newly diagnosed myeloma patients,[7–10] whereas F-Δ13 is found in approximately 50% of the same population.[3,11,12] This discrepancy is because the former technique is reliant on proliferating myeloma cells to generate a result, whereas the latter is independent of cell division. The second concept is a derivative of the first: M-Δ13 is a composite prognostic marker because it provides information about both proliferation and the chromosome 13 structural abnormality.[13] The controversy revolves around the point that although M-Δ13 is universally accepted as an adverse prognostic factor,[6,7] the extent deletion F-Δ13 plays as an independent adverse prognostic factor is in question.[9,14]

The paper by Jagannath *et al.*[1] explores whether bortezomib can overcome the adverse impact of deletion 13 using patients' data from the SUMMIT and APEX trials, two trials studying the role of bortezomib in relapsed/refractory myeloma patients. Although together, the two trials included 535 patients receiving bortezomib, only 221 and 102 had evaluable metaphase cytogenetics or FISH studies, respectively. In retrospective matched pair analyses using a fraction of these patients, the authors found that bortezomib provided outcomes (response rates, time to progression and overall survival) in M-Δ13 patients comparable to those patients without M-Δ13 in both trials (Table 1). In contrast, patients enrolled on the APEX trial, who received single-agent dexamethasone and had M-Δ13, did significantly poorer than those without the abnormality. At first blush, the relative equivalence seen in patients with and without M-Δ13 could be brushed aside by the possibility that this merely reflects a type II error – that is, the sample size and duration of follow-up are just too short to reveal the statistical difference between patients with and without M-Δ13 who received bortezomib. This criticism, however, is partially mitigated by the profound difference seen in dexamethasone-treated patients with and without M-Δ13. Even with the limitations of small sample size and short follow-up, outcomes associated with the presence of M-Δ13 in the dexamethasone-treated patients were far worse than in its absence. So, based on these M-Δ13 data, one can speculate that even if bortezomib does not completely level the playing field for M-Δ13 patients, it appears to reduce partially the disadvantage. The authors appropriately concede that their results need to be confirmed by others.

A twist to the Jagannath *et al.*'s paper arises when the same case-matched analyses were performed by using FISH in the presence or absence of deletion 13. Again, there was no significant difference in outcome for those bortezomib-treated patients with and without F-Δ13; however, no difference was seen in dexamethasone-treated patients with and without F-Δ13 either! How does one reconcile the differences between the M-Δ13 and F-Δ13 analyses in the Jagannath *et al.*'s study? Their FISH results would appear to challenge the argument offered in defense of the M-Δ13 findings. Perhaps, the difference can be explained, in part by the differential prognostic impact F-Δ13 has as compared to M-Δ13, that is, proliferation – or perhaps, these inconsistencies are all a function of small sample size.

Moreover, the paper by Sagaster *et al.*[2] in this issue supports the findings of Jagganath *et al.*, in that Sagaster *et al.* also find that overall response and time to treatment failure are not different in bortezomib-treated patients regardless of deletion 13 status (Table 1); however, in this latter study, there was a trend toward inferior survival in the F-Δ13 patients as compared to those without the abnormality. In addition, Sagaster *et al.* make the provocative observation that all three patients with t(4;14) responded to bortezomib and they propose a risk classification system incorporating deletion 13 and serum albumin. A major caveat to this study is that the patients with F-Δ13 may have had other prognostic factors that influenced their overall outcomes. Take for example, the fact that the time from diagnosis was only 26 months for the F-Δ13 patients in contrast to 51 months for the patients without the deletion. Is this imbalance because patients with F-Δ13 have shorter times to progression and therefore have exhausted other treatments more quickly, or is it due to the fact that the group of F-Δ13 patients who responded to bortezomib were earlier along in their disease course? These are questions that cannot be answered by this small retrospective review. A recent publication by Mateos *et al.*[16] also bolsters the favorable influence bortezomib may have on F-Δ13 patients. With 16-month follow-up, they reported that newly diagnosed, elderly myeloma patients treated with VMP demonstrated no difference in PFS for those patients with and without F-Δ13 (Table 1).

The final paper in this issue of *Leukemia* that deals with cytogenetic abnormalities in myeloma patients is that of Gutiérrez *et al.*[2] These authors analyze the FISH findings of 260 newly diagnosed patients participating in an HSCT trial and scrutinize the role F-Δ13 plays as a prognostic factor in patients with other FISH abnormalities. The authors probed for retinoblastoma gene deletion (standard surrogate for F-Δ13), chromosome 14 translocations and the p53 deletion F-Δ17p51. Their analysis is a complicated one, with multiple comparisons and sub-analyses. The authors report that F-Δ13, F-Δ17p51 and 14q32 translocations had significant adverse impact on time to progression and overall survival on univariate analysis, but go on to further dissect the role other abnormalities have on F-Δ13's impact on survival by whittling the 109 patients with F-Δ13 down to 46 patients without any of the other FISH abnormalities (14q32 translocations or F-Δ17p51) and report that median overall survival for these 46 patients was not

Table 1 Effect of bortezomib therapy on patients with deletion 13[1,2,15]

Treatment	*Abnormality*	N	*TTP (mo)*	*P-value*	*MS (mo)*	*P-value*
Bortez-SUMMIT[1]	M-Δ13	26	2.6	NS	10	NS
Bortez –SUMMIT[1]	No M-Δ13	26	3.3	—	NR	—
Bortez -APEX[1]	M-Δ13	64	2.6	0.06	12.5	0.8
Bortez -APEX[1]	No M-Δ13	64	7.7	—	NR	—
Dex[1]	M-Δ13	61	2.8	0.2	3.3	0.002
Dex[1]	No M-Δ13	61	5.6	—	NR	—
Bortez -APEX[1]	F-Δ13	18	6.2	0.2	NR	NE
Bortez -APEX[1]	No F-Δ13	18	4.6	—	NR	—
Dex[1]	F-Δ13	20	3.5	0.6	NR	NE
Dex[1]	No F-Δ13	20	2.8	—	NR	—
Bortez[2]	F-Δ13	33	4.6[a]	0.95	9.9	0.057
Bortez[2]	No F-Δ13	29	6.7[a]		NR	
VMP – newly Dx[15]	F-Δ13	13	92% at 1 year	NS	NP	—
VMP – newly Dx[15]	No F-Δ13	20	91% at 1 year	—	NP	—

Bortez, bortezomib; Dex, dexamethasone; F-Δ13, deletion 13 by FISH; M-Δ13, deletion 13 by metaphase cytogenetics; mo, months; MS, median overall survival; NE, not evaluable; NP, not provided; NR, not reached; NS, not significant; TTP, time to progression; VMP, bortezomib, melphalan, prednisone.
[a]Time to treatment failure.

significantly different than the overall survival of the 109 patients without any FISH abnormality (54 versus 46 months). This is an interesting finding, but the authors' conclusion that 'Rb deletion as a unique abnormality is not associated with adverse prognosis', is too strong given the limitations of their data. The median follow-up for these patients is only 34 months, and, therefore, conclusions about portions of survival curves distant from median follow-up should be tempered, especially when there are pre-existing data from larger studies that show contradictory findings. Earlier this year, in this journal, Chiecchio *et al.*[6] studied 729 patients by FISH, 81% of whom were newly diagnosed. They reported that the median overall survivals of patients with different FISH abnormalities were significantly different: no F-Δ13, median overall survival not reached; F-Δ13 as the only abnormality, 29 months; F-Δ13 with either an 14q32 translocation or FΔ17p51, 20 months; and F-Δ13 with both an 14q32 translocation and FΔ17p51, 13 months. Chiecchio *et al.*'s study also has limitations, that is, no treatment information and a median follow-up of only 22 months.

So what can we conclude from these three studies in this issue of *Leukemia*? They provide important hypothesis generating ammunition. Based on the data of Jagannath *et al*[1]and Sagaster *et al.*,[2] we need to further test the hypothesis that bortezomib may have a favorable influence on patients with M-Δ13, which may be a function of deletion of the retinoblastoma gene and/or a function of the proliferative index of the myeloma cells. The Gutiérrez data provides us with confirmation that t(4;14), 17p51 and F-Δ13 carry significant adverse prognostic influence in patients undergoing stem cell transplantation.[6,8,16–19]

These studies also underline the fact that a uniform, practical cytogenetic staging system is needed and should be defined by the myeloma community. Although the International Staging System,[20] which uses beta-2 microglobulin and albumin, has been a major step forward in the direction of 'speaking the same prognostic language', the myeloma community is ready for more. Already it has been shown repeatedly that in patients with multiple myeloma, deletion 13 is the most common monosomy,[21] that there is a strong association between it and 14q32 translocations,[12,22] that t(4;14) is among the worst-recognized translocations[17–19,23] and that deletion 17p51 also has prognostic implications.[8,17,24–26] Perhaps a similar meeting of the minds as used for the International Staging System could be arranged to finalize a practical, internationally accepted cytogenetic staging system that can be used in clinical practice.

At present, what are the implications for the clinician taking care of a myeloma patient? All newly diagnosed patients (and all clinical trial patients) should have both a standard metaphase karyotypic analysis performed as well as a standard myeloma FISH panel. Only in this way will we be able to best educate our current patients about their individual prognosis and to understand the role novel agents and combinations play in overcoming the adverse prognostic effect of possessing an adverse cytogenetic feature for future generations of myeloma patients.

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