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Up-front ixazomib in older patients with myeloma

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In this issue of *Blood*, Facon et al report the results of the large randomized Tourmaline 2 trial including 705 transplantation-ineligible patients with newly diagnosed multiple myeloma, in which they show that the addition of oral ixazomib to the standard-treatment doublet of lenalidomide plus low-dose dexamethasone (Rd) results in a clinically meaningful progression-free survival (PFS) benefit.[1]

It has already been shown that, compared with doublets, triplets including a proteasome inhibitor and an immunomodulator significantly improve PFS in multiple myeloma, both in patients with relapsed disease[2] and in newly diagnosed patients (including transplantation-eligible[3] and -ineligible patients[4]). Therefore, the standard of care is the combination of bortezomib plus Rd (VRd). However, the high incidence of bortezomib-induced peripheral neuropathy often prevents long-term administration. Therefore, evaluating the efficacy and safety of the 2 other approved proteasome inhibitors, carfilzomib and ixazomib, is important

The recently published randomized trial Endurance showed that, in newly diagnosed patients without high-risk cytogenetics, the addition of carfilzomib at a dose of 36 mg/m^2 to Rd compared with VRd did not improve PFS and was slightly more toxic.[5] Ixazomib is less neurotoxic than bortezomib and less cardiotoxic that carfilzomib and is administered orally.[6] Therefore, the combination of ixazomib plus Rd (IRd) might be an attractive alternative to VRd, especially in older patients.

Although the PFS benefit in the ixazomib arm of the Toumaline 2 trial was a clinically relevant 13.5-month improvement (35.3 vs 21.8 months; hazard ratio [HR], 0.83), it did not reach statistical significance ($P = .073$), and the results in the Rd control arm were relatively modest compared with those in other randomized trials with Rd[4,7,8] (21-34 months; see table). The differences in outcome among Rd-treated patients may be explained by differences in study design and initial patient characteristics. Induction in the Toumaline 2 trial, with 18 28-day IRd cycles, was well tolerated. However, there was a slight increase in early deaths (within 6 months) in the ixazomib arm. Also, PFS was not improved in patients age ≥75 years. These findings may suggest that this triple combination should be used cautiously in elderly frail patients. The impact of the maintenance treatment with a combination of ixazomib and lenalidomide compared with lenalidomide alone cannot be assessed from this report.

Although cross-trial comparisons are always hazardous, the complete response rate with IRd (25.6%) was identical to that achieved in the SWOG VRd trial (24.2%). Although the median PFS was 6 months shorter with IRd, the study population was much older. Compared with the Endurance trial, conducted in patients with only standard-risk cytogenetics and a lower median age, the PFS achieved with IRd was quite similar to that achieved with carfilzomib plus Rd (34.6 months) or with VRd (34.4 months).[5] Therefore, this all-oral triplet with ixazomib is a viable alternative to other proteasome inhibitor–based triplets, especially when long-term injection treatment or frequent trips to the hospital (especially during the COVID-19 pandemic) are of concern for patients. Interestingly, there was also a significant PFS benefit in patients with high-risk cytogenetics (including amp[1q21]), which confirms the efficacy of ixazomib in this subgroup of patients, as previously shown in relapsed multiple myeloma.[6]

In addition to the specific results of the trial, several general questions are pertinent with regard to this study. Firstly, these results highlight the frequent problem faced in the interpretation of the word significance in clinical trials, because "not statistically significant" is often misinterpreted as "not clinically important," whereas statistical significance, which is affected by the sample size and end points of a study, must be differentiated from clinical relevance or importance.

Secondly, the PFS benefit in the ixazomib arm was due to a higher complete remission rate (26% vs 14%) and a higher response rate of very good partial response or better (63% vs 48%). However, with a median follow-up of >50 months, the overall survival (OS) curves were superimposable. With longer follow-up, would the higher incidence of negative minimal residual disease with ixazomib (15% vs 7%) translate to longer OS? It is much more likely that there will never be an OS benefit with up-front IRd, because the number of active combinations for the treatment of relapse has increased dramatically in the past few years. In particular, OS was slightly better for patients who did not initially receive ixazomib when proteasome inhibitors were used for treatment of first relapse. This may suggest that, if OS is the primary objective, saving proteasome inhibitors for salvage treatment in transplantation-ineligible patients may be a valuable and possibly less expensive alternative. Studies should be designed to evaluate the efficacy and cost-effectiveness of different therapeutic sequencing.

Finally, results of this trial (which was initiated in 2013) should be analyzed in light of more recent randomized trials evaluating the addition of daratumumab to standard treatments for transplantation-ineligible patients with newly diagnosed myeloma. The Alcyone trial showed that the addition of daratumumab to the standard combination of bortezomib, melphalan, and prednisone plus maintenance treatment with daratumumab not only dramatically improved PFS (median, 36.4 vs 19.3 months; HR, 0.42) but also significantly improved OS, with a median follow-up of only 40 months (36-month OS rate, 78% vs 68%; HR, 0.60).[9] The Maia trial

Randomized trials with Rd as frontline treatment for transplantation-ineligible patients with myeloma

Induction (duration)	First[1]		SWOG S077[4]		Endurance[5]		Tourmaline 2[1]		Maia[8]	
	Rd continuous	Rd 72 w (18 cycles)	Rd 24 wk	VRd 24 wk	VRd 36 wk	KRd 36 wk	Rd 72 wk	IRd 72 wk	Rd continuous	DRd 24 wk
No. of patients	535	541	261	264	542	545	351	354	369	368
Maintenance	Rd continuous	No	Rd continuous	Rd continuous	Len continuous or 2 y	Len continuous or 2 y	Len continuous	Ixa + Len continuous	Rd continuous	DRd 2 y then Dara continuous
Age, y	Med, 73 >75 y, 35%	Med, 73 >75 y, 36%	≥65 y, 47%	≥65 y, 39%	Med, 64 ≥70 y, 31%	Med, 65 ≥70 y, 32%	Med, 74 ≥75 y, 44%	Med, 73 ≥75 y, 43%	Med, 73 ≥75 y, 43.5%	Med, 74≥75 y, 43.6%
High-risk cytogenetics, %	17	20	NE	NE	0	0	17.8	17.1	13.6	15
Med PFS, mo	26	21	29	41	34.4	34.6	21.8	35.3	34.4	NR 60% at 30
≥CR, %	22	20	12.1	24.2	15	18	14.1	25.6	24.9	47.6
≥CR + VGPR, %	48	47	53.2	74.9	65	75	47.7	63	53.1	79.3
OS, mo	Med, 59.3	Med, 62.3	5 y, 56%	5 y, 69%	3 y, 84%	3 y, 86%	NR at 58	NR at 58	3 y, 70%	3 y, 80%

CR, complete response; Dara, daratumumab; DRd, daratumumab plus Rd; Ixa, ixazomib; KRd, carfilzomib plus Rd; Len, lenalidomide; Med, median; NE, not evaluated; NR, not reached; VGPR, very good partial response; VRd, bortezomib plus Rd.

also showed a significant improvement with the addition of daratumumab to continuous Rd, another standard frontline treatment in elderly patients, with a complete remission rate of 47.6% (vs 24.9%) and a 30-month PFS rate of 70.6% (vs 55.6%; HR, 0.56).[8] A recently updated analysis of this trial confirms that unprecedented PFS rates may be achieved with this approach (60% at 4 years).[10] Therefore, in countries where these combinations will be approved and reimbursed, combinations including daratumumab (or other anti-CD38 antibodies) will likely become the first option for transplantation-ineligible patients with newly diagnosed myeloma.

Conflict-of-interest disclosure: J.-L.H. has received honoraria from GlaxoSmithKline and Janssen. M.M. has received research support and lecture honoraria from Adaptive, Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen, Jazz, Novartis, Pfizer, Sanofi, and Takeda. ■

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DOI 10.1182/blood.2021011262

LYMPHOID NEOPLASIA

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Poor prognosis is ZAP70'ed into focus in CLL

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In this issue of *Blood*, Chen et al[1] explored the biology underpinning the relationship between expression of ZAP70 and poor disease prognosis in chronic lymphocytic leukemia (CLL). They provide compelling evidence that this tyrosine kinase facilitates CLL progression by promoting malignant cell survival and ability to remodel the microenvironment, and by increasing malignant cell capacity for protein synthesis (see figure). This work thereby lays a solid foundation stone for our understanding of the role ZAP70 plays in CLL.

ZAP70 is a tyrosine kinase that typically functions to mediate proximal T-cell antigen receptor signaling. However, changes in the way the promoter of this gene is methylated in the malignant cells of CLL lead to aberrant expression that correlates with unmutated *IGHV* gene status and poor disease outcome. Early studies on the function of ZAP70 in CLL cells showed that it enhanced BCR signaling in a way that was independent of its kinase function,[2] whereas later studies reported on the relationship between ZAP70 expression and CLL cell migration and ability create a supportive microenvironment.[3] The current study ties these observations together with a series of neat biochemical experiments.

Studying the function of ZAP70 in primary CLL cells is problematic because specific inhibitors against this kinase do not exist, and the short life span of primary cells in culture make short interfering RNA-mediated knockdown of proteins with a long half-life difficult. To overcome this problem, the authors' unique approach is to build on their previous work studying a murine stromal cell line, EL08-1D2, where they show that coculture protects CLL cells from spontaneous apoptosis.[4] Although this system stimulates WNT signals in CLL cells, it does not affect their surface expression of immunoglobulin M, which is important because this parameter can change and affect induced signaling when these cells are exposed to cytokine.[5] Furthermore, when CLL cells are removed from this coculture system, they regain their susceptibility to spontaneous apoptosis. This leads to the demonstration that ZAP70 expression protects CLL cells from spontaneous apoptosis in the absence of BCR engagement. This is a new finding made more interesting by the authors' observation that reduction of ZAP70 using short interfering RNA did not overtly affect the strength of induced BCR signaling in their system, an observation that is at odds with a previous study investigating such signaling in $ZAP70^+$ and $ZAP70^-$ CLL cells and in CLL cells that ectopically express ZAP70.[2] What is intriguing here is that the current manuscript demonstrates ZAP70 association with proteins involved with the signalosome that is formed in CLL cells upon engagement of BCR, raising a question of whether ZAP70 is a nonfunctional bystander in the traditional BCR pathway as we know it. Indeed, this may not be the true function of ZAP70 in this context at all, and the authors provide data showing that induced BCR signaling facilitates interaction of this kinase with ribosomes, where it promotes protein synthesis potentially through association with, and phosphorylation of, ribosome binding proteins such as RPS-17. This is a function specific for ZAP70; the authors show that its paralog, spleen tyrosine kinase, does not associate with these proteins in CLL cells and could also result from weak BCR signals or other stimuli because ZAP70-dependent protein synthesis occurs in CLL cells that are not subject to overt BCR engagement. The cause of such weak BCR signals or stimuli needs further clarification, but could be the consequence of a feedback loop initiated by innate immune signals that the current group previously reported in which secreted immunoglobulin M is able to autorecognize BCR on the surface of $ZAP70^+$ CLL cells.[6] Whatever the cause, it is highly probable that this is where ZAP70 plays its most important role, and the data presented show this kinase regulates constitutive activation AKT and gene expression of MYC, CCL3, CCL4, and interleukin 4-induced gene-1 (IL4I1). Thus, weak tonic activation of ZAP70 in CLL cells increases their fitness to survive and proliferate where CCL3, CCL4, and IL4I1 act to recruit T cells and macrophages and help them provide a supportive environment for CLL cells, and where increased levels of MYC in CLL cells drives enhanced proliferation (see figure). How such activation of ZAP70 is connected to unmutated *IGHV* gene status in CLL now needs to be investigated to determine why expression of this kinase cannot be established as an independent prognostic indicator in this disease.

Now that we more clearly understand the function of ZAP70 expression in CLL, an important question is whether this could be exploited therapeutically. The answer is potentially yes, because cells that have high levels of protein synthesis require essential amino acids to build these proteins. This is supported by studies showing that patients with aggressive CLL have lower levels of serum methionine,[7] that CLL cells are acutely sensitive to the absence of cysteine,[8] and that higher IL4I1 expression by CLL cells likely increases their catabolism of tryptophan.[9] Ultimately, this means that although ZAP70 expression enhances CLL cell fitness, it also exposes them to a need that can be exploited.