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● ● ● **CLINICAL TRIALS**

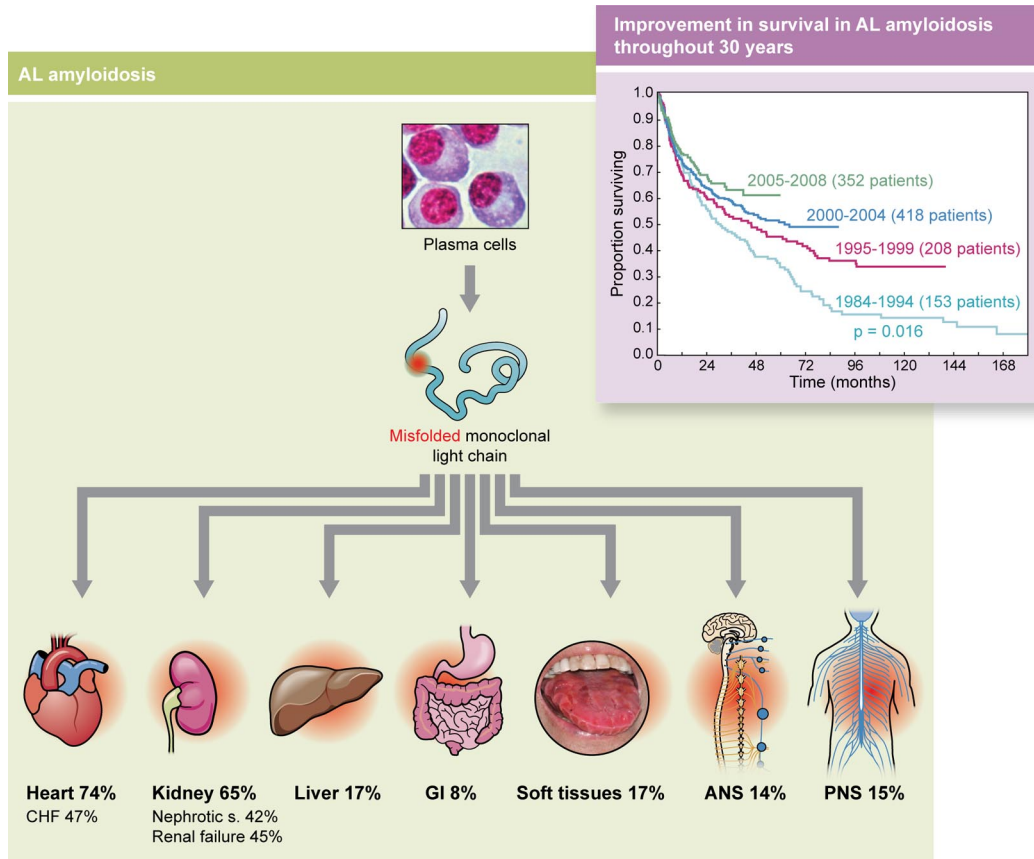
Comment on Mikhael et al, page 4391, and on Venner et al, page 4387

CyBorD: stellar response rates in AL amyloidosis

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In two independent retrospective studies, Mikhael et al and Venner et al report unprecedentedly high hematologic response rates, 94% and 81%, including complete response (CR) in 71% and 42%, respectively, to the combination of cyclophosphamide-bortezomib-dexamethasone in patients with either naive or relapsed light chain (AL) amyloidosis.^{1,2}

Light chain amyloidosis is caused by a small or modest, relatively indolent, plasma cell clone synthesizing misfolded light chains. These abnormal light chains behave like “sick molecules,” a term coined by Jan Waldenström, because they display a pathologic conformation prone to aggregation and become toxic for cells and tissues, producing devastating systemic damage (see figure). λ light chains are more prone to misfold than are κ light chains, and certain subgroups have been reported to be preferentially associated with specific organ targeting (eg, *IGVL1-44*



AL amyloidosis is caused by a small or modest, relatively indolent, plasma cell clone secreting light chains (ratio of λ to κ light chains, 4:1) with abnormal folding (misfolded) caused by mutations (symbolized by red dot) that affect critical structural sites. These light chains are prone to aggregation, form amyloid fibrils, and become toxic for cells and tissues, producing failure of vital organs. Heart involvement is the most clinically relevant because it is the cause of death in virtually all patients. Inset: Survival of 1131 patients with AL amyloidosis according to the year of diagnosis followed at the Pavia Amyloid Research and Treatment Center. Although survival continues to improve, the slope of the first part of the curves has not changed during almost 30 years, mostly because of early death of patients with severe cardiac involvement. ANS indicates autonomous nervous system; CHF, congestive heart failure defined as New York Heart Association class III or IV; GI, gastrointestinal tract; and PNS, peripheral nervous system. Professional illustration by Kenneth X. Probst.

with heart involvement).³ The misfolded monoclonal light chain can be directly cytotoxic to cardiomyocytes,⁴ and the extent of cardiac damage is a major prognostic determinant because heart failure and fatal arrhythmias are the cause of death in a substantial number of patients. Cardiac biomarkers, troponins, and particularly the natriuretic peptide type B (NT-proBNP), are very sensitive and reliable sensors of light chain cardiotoxicity and allow early assessment of cardiac response to therapy. They are also powerful prognostic determinants used to stratify the risk according to the Mayo cardiac staging system.⁵ The light chain-induced cardiac damage is progressive, but potentially reversible, unless the myocardial lesions are advanced. Improvement of cardiac function after therapy, assessed by NT-proBNP, translates into improved survival.^{6,7}

Thus, the strategy for improving survival in AL amyloidosis should be based on early detection of amyloid cardiac involvement while the damage is still reversible, and on the rapid and profound reduction of the amyloid light chain concentration to arrest the progression of the cardiac damage and rescue the heart's function. The most sensitive, although not specific, marker of early cardiac involvement is NT-proBNP, which can anticipate the onset of symptoms related to heart failure by several months.⁸ Because patients with monoclonal gammopathy of undetermined significance (MGUS) are at risk, albeit low, of developing AL amyloidosis it would be advisable that periodic checkups of individuals with this condition include measurement of NT-proBNP, to detect and treat amyloid cardiomyopathy promptly.

The goal of chemotherapy is rapid, profound, and persistent reduction of amyloid light chain concentration to rescue organ function and improve survival. Although significant progress has been made toward this goal (see figure inset) standard therapy based on melphalan and dexamethasone^{9,10} is not effective in patients with severe cardiac involvement (Mayo cardiac stage III). The dismal outcome is mainly due to the high early death rate (23%–33%), from advanced cardiac amyloidosis, in the first 2 to 3 months after starting therapy.^{9,10} These patients do not have enough time to respond to this therapy.

Since the very first investigations, it was evident that bortezomib might represent a breakthrough in the care of AL amyloidosis,

producing prompt and profound responses even in pretreated patients. The molecular basis of the high sensitivity of amyloidogenic plasma cells to proteasome inhibition is still under intense investigation. A prospective phase 1/2 study on bortezomib as a single agent in relapsed patients using either a weekly or a twice-weekly schedule resulted in hematologic response rates of 68.8% and 66.7%, respectively, including 37.5% and 24.2% CR. Bortezomib showed limited cardiac toxicity. Importantly, the median time to first response for the twice-weekly schedule was just 1 cycle.

The addition of bortezomib to an alkylating agent, melphalan, and dexamethasone further improved outcome. A phase 2 prospective study including 26 patients with AL amyloidosis showed that this regimen produced a hematologic response in 94% of patients, with 56% achieving a CR.¹¹

After impressive response rates observed in multiple myeloma, the combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD, or CVD) has been explored in AL amyloidosis. Here, Mikhael et al report the retrospective analysis of 17 patients with AL amyloidosis, 10 of whom were treatment-naïve, who were treated with a median of 3 cycles (range, 2–6) of weekly administration of CyBorD before autologous stem cell transplantation (ASCT), as an alternative to high-dose therapy for those deemed ineligible, and as salvage for relapsing patients.¹ The reported 94% of hematologic responses is excellent and the 71% CR rate unprecedented in AL amyloidosis. The estimated median duration of CR was 22 months (range, 5–30 months). Organ response was observed in 50% of patients with renal involvement. Notably, 3 patients originally not eligible for ASCT became eligible after treatment with CyBorD. Treatment was well tolerated, with only 2 patients experiencing grade 1 or 2 peripheral neuropathy, possibly thanks to the weekly schedule of bortezomib. In the London National Amyloidosis Center study by Venner et al, 43 patients (20 treatment-naïve) were treated with biweekly bortezomib and dexamethasone.² Because 46% of patients had Mayo cardiac stage III disease, both bortezomib and dexamethasone dosages were attenuated. The hematologic response rate was 81.4% with a CR rate of 39.5%. As expected, neuropathy was more frequent in this study using biweekly bortezomib, occurring in 30% of patients and resulting in discontinuation of therapy in

14%. The remarkable finding of this study was that in the 20 patients with Mayo cardiac stage III disease, the estimated overall survival at 2 years was 94.4%, thus strikingly better than the median survival with melphalan and dexamethasone, which is ~ 10 months from diagnosis.⁹ This is the first hint that the profound and rapid hematologic response induced by bortezomib may modify the course of severe amyloid cardiomyopathy.

Although the results of these 2 studies should be interpreted with caution given their retrospective design with possible selection bias, limited number, variable entry criteria, and, above all, short follow-up (median 21 months¹ and 14 months,² respectively), they clearly show that CyBorD/CVD has a profound and rapid effect on the amyloidogenic clone. Because there is strong evidence linking the quality of response to survival in AL amyloidosis,¹² CyBorD/CVD has great potential to change the natural history of the disease. The availability of this powerful regimen opens new perspectives in the care of AL amyloidosis and raises several challenging questions that should be addressed through controlled, prospective trials. First, given the sparing of stem cells with this regimen, it is uncertain whether patients who achieve CR should proceed with ASCT, in light of the risk of the procedure in these fragile individuals. Second, the rapid responses produced by CyBorD/CVD open up the possibility of thwarting the high rate of early mortality in patients with advanced cardiac amyloidosis. A European phase 2 trial using attenuated doses is being developed for patients with Mayo cardiac stage III disease. Third, the overall impact of adding bortezomib to alkylating agents front-line on the natural history of the disease should also be assessed in prospective randomized trials. Because “time is life” in this frequently rapidly progressive disease, we need to answer these important questions quickly. AL amyloidosis is a rare disease and international collaboration is needed to accrue patients in clinical trials. Through an unprecedented international effort, a randomized trial comparing the present standard of care, melphalan-dexamethasone, versus bortezomib-melphalan-dexamethasone is now under way in Europe, Australia, and in the United States. This recently established network of referral centers dedicated to AL amyloidosis is a precious resource for conducting future trials. Furthermore, investigators

working in the field of AL amyloidosis have recently defined a framework for clinical research including defining clinically relevant end points, study populations, and other criteria for collaborative clinical research that should encourage rapid testing of therapies and expedite new drug development. This framework will be formally presented in May 2012 at the XIII International Symposium on Amyloidosis at the University Medical Center Groningen before being published.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

- Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. *Blood*. 2012;119(19):4391-4394.
- Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. *Blood*. 2012;119(19):4387-4390.
- Perfetti V, Palladini G, Casarini S, et al. The repertoire of lambda light chains causing predominant amyloid heart involvement and identification of a preferentially involved germline gene, IGLV1-44. *Blood*. 2012;119(1):144-150.
- Shi J, Guan J, Jiang B, et al. Amyloidogenic light chains induce cardiomyocyte contractile dysfunction and apoptosis via a non-canonical p38alpha MAPK pathway. *Proc Natl Acad Sci U S A*. 2010;107(9):4188-4193.

- Dispenziera A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol*. 2004;22(18):3751-3757.
- Palladini G, Barassi A, Klersy C, et al. The combination of high-sensitivity cardiac troponin T (hs-cTnT) at presentation and changes in N-terminal natriuretic peptide type B (NT-proBNP) after chemotherapy best predicts survival in AL amyloidosis. *Blood*. 2010;116(18):3426-3430.
- Madan S, Kumar SK, Dispenziera A, et al. High-dose melphalan and peripheral blood stem cell transplantation for light-chain amyloidosis with cardiac involvement. *Blood*. 2012;119(5):1117-1122.
- Palladini G, Campana C, Klersy C, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. *Circulation*. 2003;107(19):2440-2445.
- Lebovic D, Hoffman J, Levine BM, et al. Predictors of survival in patients with systemic light-chain amyloidosis and cardiac involvement initially ineligible for stem cell transplantation and treated with oral melphalan and dexamethasone. *Br J Haematol*. 2008;143(3):369-373.
- Dietrich S, Schonland SO, Benner A, et al. Treatment with intravenous melphalan and dexamethasone is not able to overcome the poor prognosis of patients with newly diagnosed systemic light chain amyloidosis and severe cardiac involvement. *Blood*. 2010;116(4):522-528.
- Gasparetto C, Sanchorawala V, Snyder RM, et al. Use of melphalan (M)/dexamethasone (D)/bortezomib in AL amyloidosis [abstract]. *J Clin Oncol (Meeting Abstracts)*. 2010;28(15 suppl):8024.
- Palladini G, Dispenziera A, Gertz MAA, et al. Validation of the criteria of response to treatment in AL amyloidosis [abstract]. *Blood (ASH Annual Meeting Abstracts)*. 2010;116(21):1364.

DAP10/DAP12 molecules as well as their killing potential and started producing IL-12p40.² In vivo, MCMV infection triggered their migration to lymph nodes and their maturation into professional APCs able to cross-prime MCMV-specific CD8⁺ T cells.² After lung viral infection with influenza virus, IKDCs were recruited to lungs and were endowed with antigen-presenting capacities.⁸ Most of these studies demonstrated the intrinsic APC functions of IKDCs using adoptive transfer of IKDCs in vivo (purified from resting spleens or cultured from bone marrow in the presence of growth factors) into hosts presenting genetic defects in the MHC class I^{4,7} or class II pathway⁷ or depleted from CD11c^{high} classical dendritic cells (DCs). In these reports, IKDCs drastically differed from B220⁻ or MHC class II⁻ NK cells that failed to present antigens to naive T cells.^{2,7}

However, several arguments indicated that IKDCs may truly belong to the NK-cell lineage (as opposed to a bona fide DC origin), challenging the acronym "IKDC." First, IKDCs were dependent on IL-15, IL-2Rγ chain, and Id2 but independent of Flt3L for their in vivo differentiation.^{6,9,10} Secondly, gene- and NK receptor-expression profiling suggested that IKDCs resemble mature NK cells.⁵ Finally, many IKDC-related markers (CD11c, B220, and MHC class II) can be shared by mature NK cells, at least on in vitro activation.⁹ Therefore, a consensual view emerged as to reconsidering IKDCs as B220⁺ NK cells endowed with unique tumoricidal and/or APC potential.

In this issue of *Blood*, Guimont-Desrochers et al report that B220⁺ NK cells are a novel intermediate in NK-cell differentiation preceding the acquisition of CD27.⁵ After adoptive transfer of CD45.1⁺B220⁺ NK cells (CD11c^{int}CD122⁺) into C57BL/6 or B6.Rag1^{-/-} CD45.2⁺ hosts, B220⁺ NK cells highly proliferated and progressively adopted a mature NK phenotype (B220⁻CD43⁺CD11b^{high}). In contrast, B220⁻ or CD27⁺ NK cells failed to acquire the so-called B220 activation marker even on in vivo stimulation with Poly I:C or anti-CD40 agonistic antibodies (see figure). The high incorporation rate of BrdU as well as a transcriptional profile highlighting genes associated with cell-cycle and microtubule organization, a large size, and high levels of

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Comment on Guimont-Desrochers et al, page 4349

IKDCs or B220⁺ NK cells are pre-mNK cells

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The cell lineage origin of interferon-producing killer dendritic cells (IKDCs) has been challenged since 2006 when the unique capacity of these cells to accumulate in tumors and mediate remarkable antitumor effects was first described.¹⁻⁴ In this issue of *Blood*, Guimont-Desrochers et al redefine B220⁺ NK cells as a novel intermediate in NK-cell differentiation preceding the acquisition of CD27.⁵

IKDCs were originally defined as CD11c^{int}B220⁺CD49b⁺MHC class II⁺ cells, endowed with an unexpected functional plasticity compared with classical NK cells. After in vivo exposure to imatinib mesylate and IL-2 or TLR9L, conditions of trans-presentation of IL-15Rα/IL-15, IKDCs lost MHC class II molecules and harbored potent TRAIL-dependent lytic activity

leading to immunogenic cell death of their targets.⁶ In contrast, when licensed by tumor cells, IKDCs up-regulated MHC class II and CD86 molecules and acquired the capacity to cross-present exogenous antigens to naive CD8⁺ and CD4⁺ T cells in an MHC class I- and class II-dependent fashion, respectively.^{4,7} On TLR-9 activation in vitro, IKDCs down-regulated NKG2D/