Bortezomib in the treatment of AL amyloidosis: targeted therapy?

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In the current issue of the journal four papers are dedicated to the treatment, and the related toxicity, of conditions caused by the deposition of monoclonal light chains, including AL amyloidosis and light chain cast nephropathy. In particular, the paper by Kastritis *et al*.[1] reports, for the first time, the outstanding efficacy of the proteasome inhibitor bortezomib in the treatment of AL amyloidosis.

Why are cells secreting amyloidogenic monoclonal proteins so sensitive to these drugs? Recent evidence indicates that the effect of bortezomib on myeloma cells cannot be completely explained by the inhibition of the transcription nuclear factor-κB (NF-κB), and that the stress of the endoplasmic reticulum (ER) linked to their function as secretory cells contributes significantly to their sensitivity to proteasome inhibitors. Here we discuss the possible relationships between the synthesis and secretion of misfolded proteins, cell stress and the role of the ubiquitin-proteasome system. A detailed understanding of these key pathways is bound to improve the care of patients with plasma cell dyscrasias, including those with AL amyloidosis.

Systemic AL amyloidosis is a protein misfolding disease[2] characterized by the over-production, usually by relatively small clones of immunoglobulin (Ig) secreting cells,[3] of a light chain with mutations[4] which destabilize the protein and favor its aggregation and tissue deposition.[5] The deposits are composed of amyloid fibrils, presenting a cross β supersecondary structure. The process of amyloid deposition produces tissue damage and eventually organ failure, leading to the death of untreated patients.

AL amyloidosis is a serious and complex disease, with an incidence of 8.9/million person-years. Despite severe difficulties in the diagnosis and treatment of AL amyloidosis, patients with this disease can achieve long-term survival if properly managed. Optimal management requires early diagnosis, correct amyloid typing, prompt effective treatment, close follow-up and careful supportive therapy. One of the most important determinants of outcome is early diagnosis, as severe amyloid organ disease may preclude the use of potentially effective treatment regimens. Systemic involvement affecting vital organs such as the heart, kidneys and liver renders these patients particularly fragile and sensitive to chemotherapy.

Response to treatment is a valid end-point for predicting the outcome of patients with AL amyloidosis

Differently from multiple myeloma, in which survival is determined by the tumor mass, in AL amyloidosis the progressive systemic damage is caused by the pathogenic light chain, and therefore the ultimate goal is the elimination, or significant reduction, of the offending protein in the most rapid way and with the least possible systemic toxicity.[3] The extent and rapidity of reduction of the monoclonal light chain are of paramount importance since they are closely related to outcome. Clinical evidence supports this assumption. In patients treated with non-myeloablative chemotherapy, a >50% reduction of the amyloidogenic light chain (partial remission, PR) is associated with improved survival.[6]

Our group observed that, in patients with cardiac AL amyloidosis treated with non-myeloablative chemotherapy, the reduction of the circulating light chains concentration translated in most patients into a reduction of the serum concentration of NT-proBNP, a sensitive cardiac biomarker, and improved heart function, and that the decrease in NT-pro BNP afforded by complete remission (CR) was greater than that by PR.[7] Furthermore, survival is significantly prolonged when light chains and NT-proBNP decrease, whereas patients with cardiac AL who do not respond promptly to chemotherapy are at risk of early death.[7] More recently, the Mayo Clinic Group reported that high light chain concentrations before transplantation predicted a higher risk of early death. Moreover, survival was predicted by the absolute light chain concentrations achieved after autologous stem cell transplantation (ASCT), rather than by the percent reduction.[8]

In this issue of the journal, Gertz *et al*. analyze 282 patients who underwent ASCT.[9] In agreement with others,[10,11] their results show that the degree of response, i.e. the extent of the reduction of the amyloidogenic light chain concentration, is an important predictor of survival. Patients who achieved a CR survived longer than those achieving a PR, who in turn survived longer than patients with less than a 50% reduction in light chain concentration. Furthermore, multivariate analysis showed that the only significant predictors of survival were response to chemotherapy and a cardiac biomarker, serum troponin T levels. These results are similar to those obtained in our general AL amyloidosis population in which multivariate analysis showed that cardiac involvement and response to therapy are independent prognostic determinants.[12] Hematologic response, i.e. the degree of reduction of light chain concentration, should, therefore, be considered a valid end-point in clinical trials for AL amyloidosis and efforts should be directed at

increasing the hematologic CR rate. Strategies to accomplish this include the use of new agents that have been employed successfully in the treatment of multiple myeloma, e.g. thalidomide,[13-15] lenalidomide,[16,17] or bortezomib.[18,19]

Bortezomib treatment produces a high rate of rapid responses in AL amyloidosis

In this issue of the journal, Kastritis *et al*.[1] report on 18 AL amyloidosis patients, including seven who had relapsed or progressed after previous treatments, who were treated with the combination of bortezomib and dexamethasone (BD). The remarkable findings of this study are: (i) an unprecedented hematologic response rate of 94%, including 44% CR, among evaluable patients, which translated into organ response in 28%; notably, all seven previously treated patients achieved a hematologic response; and (ii) the rapidity of the hematologic response (median 0.9 months; range, 0.7-1.5) compared to the 3.5 to 6 months of other effective treatments. Thus the BD combination seems to fulfill many requirements for optimal treatment of AL amyloidosis, providing a high response rate and fast action. The concerns regard the duration of the response and the tolerability of the treatment. The relatively limited follow-up of living patients (median 11.2 months) does not allow conclusions to be drawn on the durability of hematologic or organ response, although the hematologic or organ progression observed in five patients in a median time of 6.8 months is of concern. If the hematologic responses are durable, organ response rates could be higher than the 28% observed so far by the authors. Indeed, organ responses are time-dependent: the median time for renal responses is 1 year and such responses can be delayed up to 36 months after ASCT.[20]

Kidney response may be accelerated by bortezomib

The study by Ludwig *et al*.[21] reported in this issue of the journal suggests that bortezomib may accelerate the kidney response, not only through its rapid reduction of the monoclonal protein concentration, but also via its NF-κB inhibitory activity. These authors report reversal of acute monoclonal protein-induced renal failure by bortezomib-based therapy in five out of eight myeloma patients. In all patients, renal improvement was associated with a significant reduction of the monoclonal protein load. Toxicity was manageable, and, again, the hematologic response was rapid (median 1.4 months), confirming that bortezomib-based combination treatment is an excellent, safe choice for acute renal failure in multiple myeloma, as indicated by previous trials.[22-24] The authors suggest that bortezomib may contribute to improving kidney disease through the inhibition of NF-κB. Proteinuria, caused either by Bence-Jones protein overflow, or by amyloidosis-dependent glomerular damage, overloads the proximal tubular cells inducing the production of inflammatory and pro-inflammatory cytokines via both NF-κB-dependent and -independent pathways.[25] The end result is apoptosis of tubular cells, persistent inflammation and progressive fibrosis leading to irreversible end-stage renal failure.

Targeting NF-κB activation seems an effective means of interrupting the process of tubulointerstitial injury, as documented in animal models.[26,27] By preventing proteasomal degradation of the NF-κB endogenous inhibitor I-κB,[28] bortezomib may contribute to improving renal function both in myeloma kidney disease and in amyloid nephropathy.

Managing bortezomib toxicity

In the present issue Cavaletti and Nobile-Orazio[29] review the sensitive issue of bortezomib toxicity, warning clinicians to be prudent. Neurological toxicity, to either the peripheral or autonomous nervous system, is the main reason for interrupting or adjusting bortezomib administration. However, this is a cumulative, dose-related adverse effect. Careful monitoring, with prompt dose reductions, as applied in the study by Kastritis *et al*.,[1] can allow continuation of therapy with an overall hematologic benefit and minimize side effects. Although dose reductions and extending the intervals between infusions are the mainstays for preventing the worsening of neuropathy, the observation that a few patients benefited from lenalidomide, with symptomatic improvement of peripheral neuropathy, is worth further investigation.[30]

Bortezomib: delivering the final blow to plasma cells on the edge?

As mentioned earlier, the particularly relevant findings of the study by Kastritis *et al*.[1] are the high rate of response to bortezomib and the rapidity of the responses (Figure 1). Why are clonal cells secreting amyloidogenic immunoglobulin so sensitive to this drug?

Bortezomib is a potent and selective inhibitor of the 26S proteasome,[31,32] a multisubunit protein complex present in all eukaryotic cells[33] which carries out the regulated degradation of ubiquitinated proteins.[34] In addition to damaged or aberrant proteins, proteasomes degrade proteins involved in the regulation of cell-cycle progression, oncogenesis, and apoptosis.[35] The proteasome plays a fundamental role in NF-κB activation through the degradation of I-κB.[28] Proteasome inhibition stabilizes I-κB, leading to NF-κB inhibition. This latter function is often invoked to explain the efficacy of bortezomib against multiple myeloma (MM). Constitutive NF-κB activity mediates MM cell survival as well as resistance to chemotherapy and radiotherapy,[36,37] by multiple mechanisms, including the induced expression of anti-apoptotic proteins, adhesion molecules, and autocrine growth factors.[38-40] However, bortezomib inhibited MM cell proliferation more efficiently than a specific IκB kinase inhibitor, PS-1145,[37,41] suggesting that proteasome inhibitors affect additional pathways.

Stress in the antibody factory

Mature plasma cells are terminally differentiated elements of the B lymphocytic lineage with a highly developed endoplasmic reticulum (ER) specialized in Ig secretion. Each of them masters the synthesis, assembly and secretion of thousands of antibodies per second[42-44] (Figure 2). As in all cells, misfolded or orphan proteins are recognized and prevented from proceeding to the Golgi by the ER quality control systems.[45] The accumulation of misfolded proteins in the ER lumen initiates a multidimensional signaling cascade known as the unfolded protein response (UPR).[46-48] Several mechanisms are activated to cope with unfolded proteins: first, translation is attenuated. The transcription of genes enhancing protein folding (ER resident chaperones and folding enzymes) and degradation (ERAD) is then increased, while the entry of proteins into the ER[49] and the stability of mRNA encoding secretory proteins[50] are selectively inhibited. If these measures are not sufficient for eliminating misfolded proteins from the ER, apoptotic pathways are activated.[51-56] Much is being learned about the mechanisms that shift an adaptive UPR into a maladaptive response, ultimately leading to cell death.[57]

Perhaps not surprisingly in view of the physiological role of plasma cells as professional Ig secretors, certain UPR genes are essential for plasma cell differentiation, Ig synthesis and survival (refs. #44, 58 *and references therein*).

Somewhat unexpectedly, when the protein production facilities increase to satisfy abundant Ig synthesis, proteasome capacity decreases during plasma cell differentiation.[58] In correlation with impaired proteolysis, poly-ubiquitinated proteins accumulate, certain death-inducing proteins are stabilized and hypersensitivity to proteasome inhibitors ensues, prior to spontaneous apoptosis.

The fall in proteasomal levels is even more striking when plasma cell differentiation is obtained *in vivo* by injecting lipopolysaccharide into mice.[58] An excessive load (Ig synthesis, part of which is bound to be defective) on a reduced proteasomal capacity makes Ig-secreting cells hypersensitive to bortezomib.[58] That the professional activity of plasma cells, i.e. exuberant Ig production, sensitizes them to proteasome inhibitors is further supported by recent reports correlating the sensitivity of myeloma cells with Ig synthesis.[41,59] These observations led to the *load vs capacity* model correlating protein synthesis, proteolytic efficiency and sensitivity to proteasome inhibitors.[44]

Amyloidogenic plasma cells as preferential targets of proteasome inhibitors?

Since proteasomal degradation is coupled to the extraction of aberrant proteins from the ER lumen, bortezomib and other proteasome inhibitors are bound to cause ER accumulation of misfolded secretory proteins, and hence ER stress.[41] In view of the fact that prolonged ER stress causes apoptosis, these observations have profound implications for the handling of AL amyloidosis. Despite the fact that the misfolding-prone amyloidogenic light chains[5,60,61] negotiate transport across the stringent ER quality control checkpoints, they likely represent a load for the ER protein factory: the higher their production, or the more they are misfolded (as a result of the destabilization caused by peculiar somatic mutations) the stronger the UPR induction, and hence the lower the threshold for apoptosis. In this scenario, bortezomib impairs ERAD, stabilizes I-κB, Bim and Bax, and eventually the final blow is delivered. The additional stress imposed to the ER machinery by amyloidogenic light chains could, therefore, increase the sensitivity of amyloidogenic plasma cells to bortezomib. Recent observations suggest that proteolytic activity is impaired in the brains of patients with Alzheimer's disease (AD),[62,63] and several studies

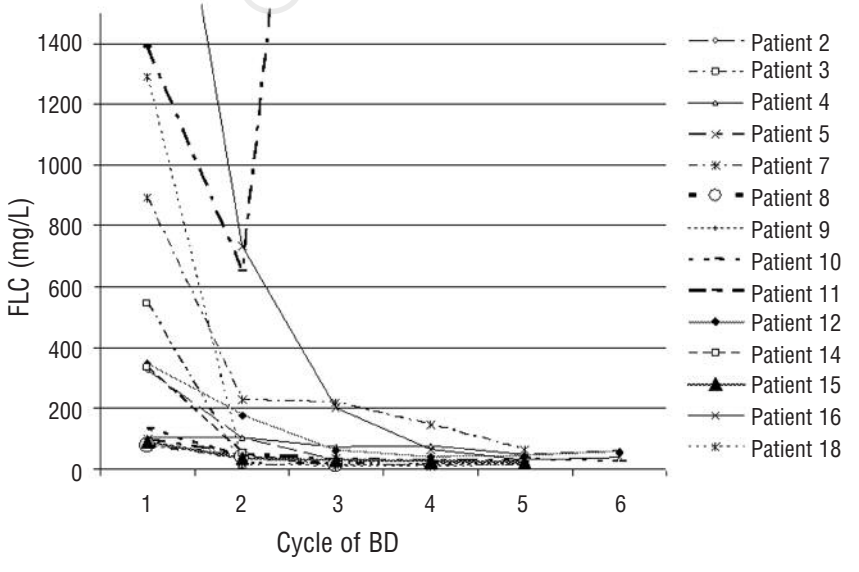

Figure 1. Involved FLC at baseline and after each cycle of the combination of bortezomib and dexamethasone (BD) in the 18 patients reported by Kastritis *et al.* in this issue of the journal.

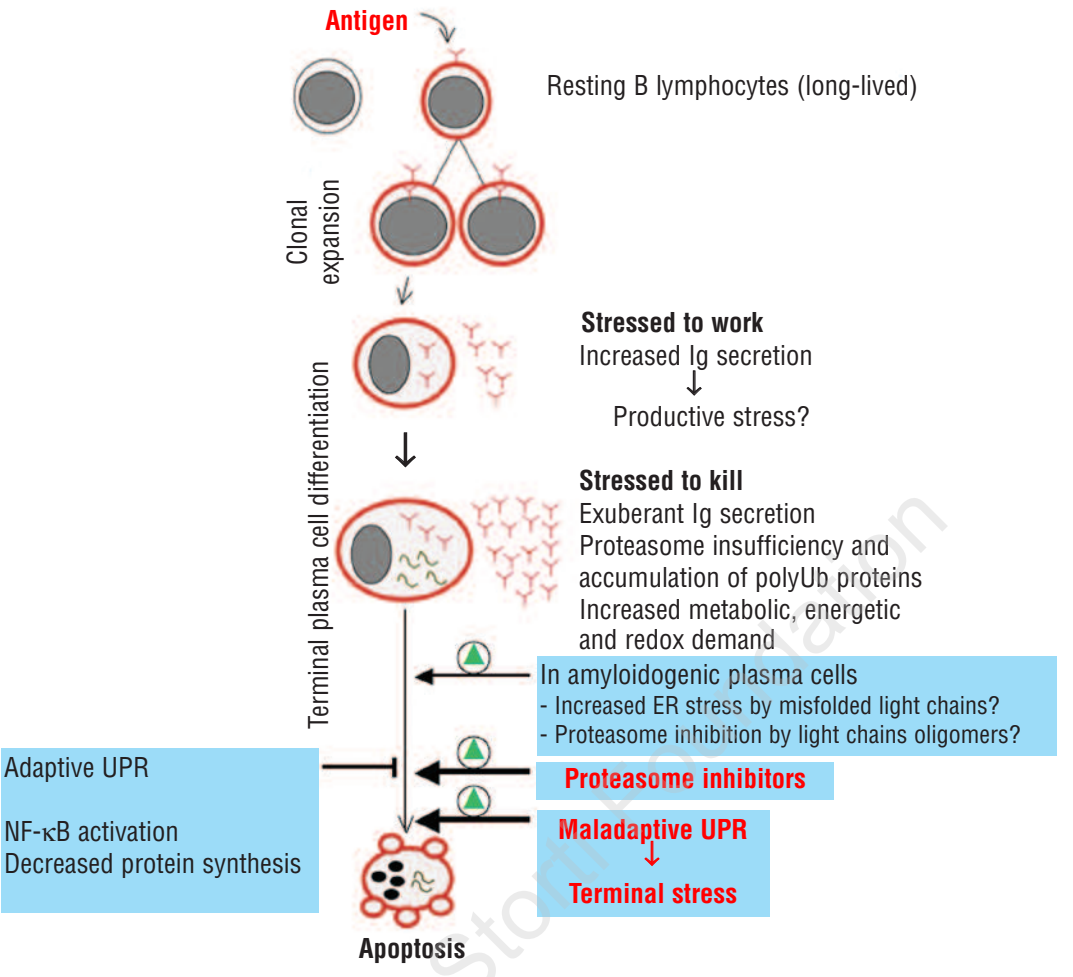

Figure 2. The dual role of stress in plasma cell differentiation. In the early stages of plasma cell differentiation, activation of *Xbp1* and other UPR-related genes is likely important for equipping differentiating B cells for the exponentially increasing secretory demand. Later on, the hectic work in the antibody factory induces ER stress, metabolic and redox imbalances and proteotoxicity, eventually leading to apoptosis. Amyloidogenic plasma cells could experience additional stress caused by the misfolded light chain, and may have a lower threshold for apoptosis. The inhibition of the proteasome by bortezomib exaggerates ER stress, blocks NF-κB activation, further stabilizes pro-apoptotic factors, eventually causing apoptosis. In the proposed scheme, attenuating Ig synthesis would reduce stress and prolong survival. Unlike in MM, this could be a goal in AL management. *Adapted from Cenci & Sitia.*[44]

have shown that Aβ protein inhibit the proteasome[64-66] and that this inhibition may be mediated by Aβ oligomers.[67] Furthermore, extracellular aggregates of another amyloidogenic protein, human islet amyloid polypeptide, impair the ubiquitin-proteasome pathway resulting in ER stress-mediated pancreatic β-cell apoptosis.[68] In analogy with these observations, extracellular oligomers of amyloidogenic light chains could inhibit proteasome activity, sensitizing amyloidogenic plasma cells in a sort of autocrine inhibitory loop. These hypothesized mechanisms, i.e. additional ER stress caused by misfolded light chains and the inhibitory loop, makes the amyloidogenic plasma cell clone strive for survival and may account for its usual small size.[3] However, it should be noted that the existence and the putative biological role of light chain oligomers are at the moment only hypothesized on the basis of clinical clues and preliminary experimental evidence. The clarification of this issue would be highly rewarding because soluble, prefibrillar aggregates might play a direct role not only on tissue toxicity but also in the cellular response to new drugs which interfere with protein processing and metabolism.

In conclusion, both extracellular oligomers of the amyloidogenic light chain, and the accumulation of misfolded light chain in the ER may act synergistically to over-stress the amyloidogenic plasma cells transforming them into primary targets of proteasome inhibitors. Several therapeutic strategies targeting other sensitive components of the ER synthetic machinery, such as inhibition of the aggresome[69] and of heat shock proteins[70] can be combined to deliver the final *coupe de grace* to amyloidogenic plasma cells.

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