Bortezomib for AL amyloidosis: moving forward

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Reece et al report that single-agent bortezomib resulted in hematologic responses in two-thirds of patients with relapsed Light chain (AL) amyloidosis, including complete responses in one-third, while more than 75% of patients had response duration of more than or equal to 1 year.1

Small plasma cell clones can cause big problems2; this could be the outline for AL amyloidosis. AL amyloidosis is the most common form of systemic amyloidosis, a protein misfolding disease that is characterized by the failure of the amyloidogenic monoclonal light chain to adopt a soluble conformation. This misfolding leads to the formation of a precursor protein that tends to form highly organized fibrils that acquire a β pleated secondary structure and form amyloid fibrils that are deposited in various tissues and organs. The formation and deposition of amyloid fibrils is a complex procedure that involves cellular quality control mechanisms, local physicochemical conditions, extracellular matrix, and the specific properties of the amyloidogenic protein, related to its primary aminoacid sequence.3 The plasma cell clone is usually small or modest, relatively indolent, and often produces very small amounts of monoclonal light chains. The resulting clinical syndromes are related to the pattern of amyloidotic organ involvement and the amyloid load in involved organs. Patients who die of AL amyloidosis do so because of complications related to amyloidotic organ involvement. Based on our current knowledge of the disease, treatment for AL amyloidosis should aim at 3 different processes: the production of the amyloidogenic protein, the formation of the amyloid fibril, and the reabsorption of the deposited amyloid fibrils. So far, there are no clinically available treatments that target the latter 2 processes. Thus, targeting the production of the amyloidogenic protein has been the mainstay of treatment for AL amyloidosis. Therapies based on alkylating agents with standard-dose corticosteroids have not been very effective. For a subset of patients, high-dose melphalan with autologous stem cell transplantation results in long-lasting remission and often in significant improvement in the function of involved organs.2,4 The combination of melphalan and dexamethasone is considered a form of standard treatment for AL amyloidosis today. However, the treatment of this disease is not satisfactory. Several peculiarities make the management of AL amyloidosis challenging. AL amyloidosis is a rare disease, and large, randomized studies are extremely difficult to conduct. The management of patients with AL amyloidosis is a challenge for every physician. Most patients present with impaired function of 1 or more organs and if

A small plasma cell clone produces poor quality amyloidogenic light chains that, mostly outside the plasma cell, tend to misfold and form amyloid fibrils (A). Inside the plasma cell the increased protein load induces ER stress and mechanisms to retain homeostasis require the rapid clearance of these proteins. The degradation of these poor quality proteins is largely dependent on proteasome activity. Bortezomib blocks proteasome degradation of proteins and increases poor quality protein load within ER thus inducing ER stress beyond the capacity of the control mechanisms and resulting in plasma cell apoptosis (B).
the heart is affected, then the prognosis is dismal. Actually, patients presenting with clinically evident heart failure and elevated cardiobiomarkers have a median survival of just a few months. With current treatments, there is often not enough time for any active therapy to reverse the clinical course.

Yet the plasma cells that produce amyloidogenic light chain may have an Achilles’ heel. Preclinical data indicate that misfolded amyloidogenic light chains increase the load that the quality control system within the plasma cell has to cope with and induce endoplasmic reticulum (ER) stress. The plasma cell is dependent on the integrity of the mechanism for the degradation of these proteins to retain intracellular homeostasis, and proteasome is central to the maintenance of this equilibrium. Blocking proteasomal degradation of proteins increases ER stress and results in cell apoptosis. Plasma cells that are producing larger amounts of immunoglobulins may be more vulnerable to the proapoptotic effect of proteasome inhibition. Bortezomib targets the activity of the proteasome and thus leads vulnerable plasma cells to apoptosis (see figure). A proof of concept for the activity of bortezomib in AL amyloidosis came a few years ago from 2 small series. The results were encouraging: bortezomib was not only active but also a fast-acting agent, even in pretreated patients. A prospective phase 1 study confirmed that bortezomib either on a twice-weekly or weekly schedule was active and safe in patients with relapsed AL and a retrospective analysis from 3 European centers highlighted the efficacy of bortezomib with or without dexamethasone. Notably, the results in previously untreated patients were very promising. In the current prospective phase 2 study by Reece et al we move another step forward: single-agent bortezomib either using 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% complete responses. Importantly, median time to first response for the twice-weekly schedule was just 1 cycle of single-agent bortezomib. Moreover, the responses were durable: > 75% of patients had response durations of ≥ 1 year in either schedule. Organ responses were also significant, especially accounting for the long-standing amyloidotic involvement in patients with relapsed AL and included 29% renal and 13% cardiac responses. However, toxicity with bortezomib in patients with AL is not negligible. Considering that most patients with AL have multiorgan dysfunction and may be quite frail, treatment with bortezomib should be carefully monitored. Fortunately, this article by Reece et al provides some guidance: a weekly schedule may be a less toxic but active regimen, although response may take somewhat longer than with the twice-weekly schedule. Nevertheless, the study did not include patients with more advanced cardiac disease, such as those with New York Heart Association class III or IV, which carry the poorest prognosis. In these high-risk patients, the results may not be as impressive, probably because organ failure predetermines the outcome.

Definitely bortezomib has the highest activity that has ever been recorded for a single agent in AL amyloidosis. The current study by Reece et al provides practice-changing data and shows the path we should follow. Bortezomib should be introduced in earlier phases of the disease: upfront bortezomib-based therapies should be the next step and we should proceed quickly. Furthermore, combination of bortezomib with dexamethasone and with an alkylating agent is likely to further enhance both hematologic and organ responses. Given the rarity of the disease, this study also shows how to move: collaborative, multinational, multicenter design is the only way to move rapidly, with well-designed phase 2 and 3 studies. AL amyloidosis is an orphan disease, and our patients have no time to spend waiting for the results of slowly accruing studies. We owe it to our patients to develop more active treatments as soon as possible.

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CLINICAL TRIALS

Comment Asselin et al, page 874

Childhood T-ALL: it’s time to move on

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The results of a randomized trial of high-dose methotrexate (HD MTX) in childhood T-cell ALL (T-ALL) reported by Asselin et al on behalf of the Children’s Oncology Group (COG) in this month’s issue of Blood demonstrate both the promise and the challenge of further improving the outcomes of children with high-risk ALL through intensified application of conventional chemotherapeutic agents. R ence nonrandomized studies in childhood T-ALL report an ~ 70% to 75% 5-year event-free survival (EFS). The trial
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