A rarely noted aspect of the era of novel agents and explosive new knowledge in the clonal plasma cell diseases is how short the half-life of relevant information has become, and how this churning has challenged clinical thinking.[1] We may, at times, lose sight of a core concept in the treatment of patients with clonal plasma cell diseases: that baseline risk to patient survival derives from two sources, the genetic endowment of the clonal cell population on the one hand, and the end organs damaged or under attack by the clone on the other.[2,3] These are the issues patients and doctors face at the bedside and in the clinic. They require clear thinking. Clonal plasma cell diseases cause organ damage and symptoms as a result. Emerging knowledge may challenge our categories but not this core concept.

For example, the categories of monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma, both of which are distinguished from symptomatic myeloma based in part on the absence of overt organ damage, differ from one another by the size of the M-protein (> 3g/dL), a variable that plays no role in the definition of symptomatic myeloma.[4] The fact that our scheme of categories is not logically compelling is further amplified by emerging knowledge from population studies that, compared with normals, MGUS patients are subject to higher incidences of bone damage and thromboembolic disease, and from phase III trial data showing that there are patients with smoldering myeloma who are at high risk for progressive organ damage over a short time span when untreated.[5–8] These challenging data have led some to become more categorical about myeloma-related organ damage or myeloma-related events, continuing to emphasize hypercalcemia, renal insufficiency, anemia, and bone damage, when clonal plasma cell diseases actually have a broad spectrum of “apps” for causing organ damage.[9] Among them are cell mass (eg, myocardial plasmacytomas), M-protein concentration (eg, hyperviscosity), and M-protein aggregation (eg, AL or monoclonal immunoglobulin deposition disease), to name only a few.

As the clinical research enterprise has grown (with 522 trials open and recruiting in the United States for myeloma as of May 10, 2011), our lapse in clear thinking has been most notably egregious in the exclusion of the sickest myeloma patients—those with the most advanced organ damage, and of the entire cadre of AL patients, from pivotal clinical trials for novel agents, and in the slowness to develop and implement useful metrics for the spectrum of myeloma-related organ damage and its reversal with therapy. In contrast, we now know that the genetic endowments of MGUS, myeloma, and AL plasma cells are remarkably similar, and that high-risk clonal plasma cell disease remains an important part of the equation in deciphering clinical studies, in diagnosing risk at baseline and relapse, and in providing patient education and care.[10]
Typing amyloidosis

Amyloidosis is a tissue diagnosis that can be made with surrogate site or involved-organ biopsies stained with Congo red.[11] Involved-organ biopsies are usually performed based on prior clinical suspicion of disease, particularly renal, gastrointestinal, or cardiac. Congo red–stained biopsy preparations from all sites are subject to error.[12] The tissue section can be cut too thin or the mounted section overstained, giving a false negative or false positive, with the results disputed by pathologists. Use of electron microscopy is helpful for confirming the presence of pathognomonic fibrils and, except for renal biopsies, is underutilized particularly when involved organs are biopsied. The first question one may face when the biopsy is read as amyloid is whether the result is reliable, and the second question one does face is that of what type of amyloid is present. Both of these questions can be answered by laser capture mass spectrometry.[13] In the hands of proteomic cytopathology specialists, Congo red–positive areas can be dissected from the slide and digested and analyzed. Amyloid deposits reliably contain the fibrillar protein (for example, lambda light chains, transthyretin, or fibrinogen A-chain) as well as fellow passenger proteins such as apo E, serum amyloid P protein, and clusterin. A false-positive sample can be clearly identified by this method.

Typing by this method is critical if a patient with amyloidosis does not have a monoclonal protein as determined by an evaluation that includes serum and urine immunofixation and the serum free light chain assay. If the patient has a monoclonal gammopathy, then the diagnosis of AL is highly likely. If the clinical picture and tempo of disease are characteristic of AL, treatment should not be delayed pending mass spectrometry typing; however, African Americans and elderly men have higher rates of both monoclonal gammapathies and other sources of amyloid proteins, namely the V122I mutant hereditary transthyretin in 4% of African Americans and “senile systemic” amyloidosis due to wildtype transthyretin in elderly men. Therefore, in these patients tissue typing by laser capture mass spectrometry is necessary even if a monoclonal gammopathy is present, and treatment should be delayed until the type is identified. Failure to diagnose a hereditary disease has implications for the patient’s kindred, while giving chemotherapy to a patient with senile amyloid confers toxicity without benefit. Once a hereditary variant has been identified, genetic testing for that variant can be used to screen and direct the counseling of family members.

Localized amyloidosis of the aerodigestive or genitourinary tracts can be a challenge. Evaluations for systemic disease with surrogate-site (for example, abdominal fat) biopsies, organ assessments, and monoclonal gammapathy testing are required to confirm the localized nature of disease. In addition, typing by laser capture mass spectrometry may be a useful aspect of the evaluation. If the localized amyloid is AL type without evidence of a systemic monoclonal gammapathy, then careful radiographic and tissue studies are indicated, seeking the cellular basis for local light chain production, for example, in a mature B cell lymphoma. Such efforts often prove unproductive, however, and patients must then be followed expectantly, and occasionally develop systemic disease over a period of years. Localized disease can be morbid. Obstructive tracheobronchial amyloid deposits may require laser therapy, while small bowel amyloid disease occasionally requires surgical resection due to obstruction or perforation.

Treating systemic AL amyloidosis

Systemic AL amyloidosis is caused by free light chains produced by clonal plasma cells or, rarely (2% of the time), by mature B-cell lymphomas.[14] Prognosis is determined by the baseline organ involvement and by the response to initial therapy.[15] In contrast to the situation in myeloma, metrics for organ involvement and response to therapy in AL have been developed over the past 15 years.[16,17] Among the most useful are the cardiac biomarkers.[18] Most patients with advanced symptomatic cardiac involvement survive less than a year from diagnosis.[19] Categorical distinctions based on plasma cell percentages have become somewhat problematic in this disease, in which at least
one-quarter of patients have more than 10% clonal marrow plasma cells.[20] In addition, the presence of high-risk clonal plasma cell disease likely affects outcome as well but has not been studied prospectively; nevertheless, cytogenetics testing and FISH (fluorescence in situ hybridization) should be performed. Thinking categorically based on the percentage of plasma cells (is this myeloma or AL or myeloma with AL?) is fuzzy and misleading regarding prognosis and therapy. Confused doctors confuse patients. Once again, the core concept applies: clonal plasma cell diseases cause organ damage and related symptoms.

Thinking clearly with that concept provides an axis for understanding and explanation. Both AL and myeloma are clonal plasma cell diseases that cause organ damage. In AL, the monoclonal free light chains are the direct vector of disease causing tissue toxicity and amyloid fibril deposits, organ damage, and clinical symptoms. [21] The free light chain assay has therefore revolutionized diagnosis and management of AL patients, because it allows us to follow the pathologic vector with each cycle of therapy. [22] Eliminating the clonal cells that make the light chains can reverse AL-related organ damage and improve the patient’s functional status. [23] Ironically, although the diagnosis of AL rests on a tissue biopsy showing apple-green birefringent fibrillar deposits when viewed under polarized light, and although the elimination of clonal cells producing the amyloid-forming light chains leads to symptomatic improvement, the tissue deposits remain in many cases, indicating that the monoclonal light chains are likely toxic in poorly understood ways and that the fibrils are the less toxic species of the pathologic protein. [24] In myeloma, the M-protein is a surrogate marker for cell mass, and reducing or eliminating the M-protein indicates the cytotoxic effect of therapy. Symptomatic improvement occurs with disease control and organ damage improves with reduced cell mass. In light chain myeloma with renal insufficiency due to cast nephropathy, however, the situation is similar to AL because of the direct effect of tubular light chain casts on the kidneys.

Stem cell transplantation for systemic AL amyloidosis

The use of stem cell transplantation (SCT) for AL evolved at a time when no available therapy could reliably produce complete hematologic responses and improve median survival by more than a matter of months. [25] The results with SCT confirmed the direct link of the clonal plasma cell disease to organ damage and survival in AL, showing that elimination of the clonal disease caused reversal of organ damage and prolonged survival. The results with SCT propelled development of metrics for organ involvement and response to therapy. We now have numerous therapies that can achieve the same results, including oral melphalan and dexamethasone and likely bortezomib (Velcade)-based therapies as well. [26–28] The sickest AL patients are not candidates for SCT. At best, 20% of newly diagnosed patients are eligible for SCT with effective doses of IV melphalan and with the expectation of a low treatment-related mortality. But why risk a 5% or 10% chance of death from therapy, and possibly worsening organ damage from toxicities of SCT, when tolerable effective combination chemotherapy is available and organ improvement can occur while the patient is undergoing treatment? Soon SCT will become a second-line therapy for those who do not respond to initial therapy and consolidation therapy for those who do. In patients treated routinely and not on a clinical trial, initial therapy is likely to contain a proteasome inhibitor in combination with other agents such as dexamethasone, as oral melphalan continues to fall from favor. The risks of myelodysplasia and secondary leukemia with monthly oral melphalan remain toxicities that patients need to understand; these risks can be diminished by using total melphalan doses less than 600 mg and certainly a total dose of oral melphalan less than 300 mg. [29]

Novel agents and clinical trials for systemic AL amyloidosis

Among the novel agents, proteasome inhibitor therapy appears to be most effective, and phase III clinical trials are assessing the combination of bortezomib and oral melphalan and dexamethasone.
versus standard oral melphalan and dexamethasone. With bortezomib, time to response of the pathologic or involved free light chains is rapid, often a month or less, and organ responses occur during therapy. The important clinical principles during therapy and in follow-up are to gauge the response of the free light chains and the metrics of organ involvement regularly and to evaluate them for concordance. Criteria for free light chain response have been defined, and with bortezomib-based therapy almost half of newly diagnosed patients can achieve strictly defined complete hematologic responses.[17,30] With weekly and likely subcutaneous dosing, the side effects of bortezomib may be further reduced and dose intensity augmented because of higher weekly doses and fewer interruptions of therapy. The major side effects of bortezomib are gastrointestinal, and range from distension, obstipation, and ileus occasionally requiring conservative in-hospital management, to transient vomiting or diarrhea.[28]

Immunomodulatory agents such as lenalidomide (Revlimid) and thalidomide (Thalomid) in combination with dexamethasone may be effective in select patients but are difficult for patients to tolerate, cause elevations in cardiac biomarkers that may be linked to cardiac-related toxicity, and have median times to response in the 3-month range.[31,32] Data regarding pomalidomide (CC-4047, Actimid) in AL are promising, and further trials with this agent are under way.[33]

Every effort should be made to enroll patients in clinical trials. Clinical trials, including multicenter phase I and I/II studies, are required to advance therapy in AL. Ideally such trials should be widely available at multiple centers. Single-center phase II trials make limited contributions to advances in therapy, particularly if both newly diagnosed and relapsed patients are eligible for the trial and time-to-event endpoints are not reported. There are several study populations among AL patients in addition to newly diagnosed untreated patients. AL patients with advanced cardiac disease, who are often excluded from clinical trials, provide a unique and unfortunate opportunity to conduct novel phase II and III trials employing overall survival as a primary endpoint, because survival in this study population can be determined in a limited timeframe. If this opportunity is seized upon in the multicenter setting (so far there have been no takers), such trials could significantly improve survival and change practice.

There is also a previously treated population of patients with relapsing disease surviving 3 or more years from diagnosis, a population which no longer contains those with advanced cardiac disease. Relapsed patients are excellent candidates for multicenter trials of novel agents in all phases. A phase I clinical trial with the novel oral proteasome inhibitor MLN9708 in AL is under way for them, and trials with other proteasome inhibitors are planned.

**Conclusions**

Risk to the survival of patients with AL largely comes from the organ damage that AL causes; however, high-risk proliferative clonal plasma cell disease can occur both de novo and at relapse in patients with AL.[34,35] Conversely, patients with myeloma can develop AL in critical organs such as the heart after years of chronic exposure to monoclonal light chains. Both situations are challenging and to some degree represent risks of prolonged survival in the era of novel agents. Thinking clearly about clonal plasma cell diseases will help us to provide more accessible explanations to patients regarding the character of their disease, and having widely available well-designed clinical trials for our patients will help us to develop more effective and, we hope, curative therapies.

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