Uniform Risk-Stratification and Response Criteria Are Paving the Way to Evidence-Based Treatment of AL Amyloidosis

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In less than a decade, the resources available to treat light chain (AL) amyloidosis have increased impressively. Physicians involved in the care of patients with this disease, which not so long ago was considered untreatable, now need to learn how best to use the many different available treatment approaches. Fortunately, in these same years our ability to identify patients at risk and to assess treatment efficacy has also greatly improved. As pointed out by Gertz and colleagues in their review article in this issue of ONCOLOGY, the initial workup of patients with systemic AL amyloidosis is founded on two pillars: unequivocal amyloid typing and careful risk assessment. Then, the therapeutic strategy should be tailored according to individual risk, and response to treatment should be closely monitored.

Initial workup of patients with AL amyloidosis

Gertz and colleagues propose the combination of serum and urine immunofixation electrophoresis and of the free light chain (FLC) assay as the first diagnostic step in patients with systemic amyloidosis. Our groups showed that all these tests are needed in order to ensure best sensitivity (98%–100%) in detecting the amyloidogenic light chain.[1,2] If a monoclonal light chain is not detected by these means, then it is unlikely that the patient has AL amyloidosis. Even if a monoclonal light chain is detected in a patient with systemic amyloidosis, however, further testing is required to demonstrate that the disease is caused by light chains.[3,4] Different types of systemic amyloidosis (AL, familial, senile, reactive to chronic inflammation) have overlapping clinical presentations, and pathognomonic signs of AL amyloidosis, such as macroglossia and periorbital purpura, are found only in a minority (6%–12%) of subjects.[5] Thus, the diagnosis of AL amyloidosis must not be presumed, and no patient should be referred for chemotherapy unless the light chain origin of the amyloid deposits has been proven.[6] To provide unequivocal amyloid typing, several sophisticated and complementary techniques are needed, including immunohistochemistry, immuno-electron microscopy, mass spectrometry, and DNA analysis[3,7–9]; these techniques are available at referral centers, and they can be rendered more widely available through national or international networks.

Once the diagnosis of amyloidosis has been established, a very simple but accurate risk stratification can be obtained by measuring cardiac troponins (cTn) and N-terminal natriuretic peptide type-B (NT-proBNP).[10] As Gertz and coworkers emphasize, the population of patients with AL amyloidosis is heterogeneous, resulting in different outcomes with the same therapy, as was the case of treatment with melphalan and dexamethasone (MDex) in different series with different extent of cardiac involvement.[11–15] Thus, patient stratification based on cardiac biomarkers should be required in all clinical trials in AL amyloidosis, in order to produce comparable results.

The choice of treatment

So far, the treatment of AL amyloidosis has been chemotherapy aimed at suppressing the plasma cell clone producing the amyloidogenic light chain. The French multicenter study comparing MDex to autologous stem cell transplant (ASCT) showed that ASCT is not superior to MDex in a general population of patients with AL amyloidosis.[12] After this study, a lively debate has arisen as to whether there is still a place for ASCT in the treatment of this disease. Like Gertz and colleagues, we still offer transplant to carefully selected subjects aged < 65 years, with normal cTn and adequate renal function, who represent 10% of our patients.[16] At our center, MDex is standard treatment for the majority of subjects, but stem cell-sparing regimens,
like the combinations of cyclophosphamide and dexamethasone with thalidomide (Thalomid) or bortezomib (Velcade),[17,18] are preferred in subjects with potentially reversible contraindications to ASCT. On the other hand, MDex cannot overcome the poor prognosis of patients with advanced cardiac AL amyloidosis, neither alone[13–15], nor combined with thalidomide,[19] and the best approach for these subjects still needs to be found. Young patients with isolated advanced cardiac involvement should undergo heart transplant followed by ASCT.[20]

New drugs are finding their place in the growing therapeutic armamentarium. In particular, the proteasome inhibitor bortezomib may represent a targeted therapy for AL amyloidosis.[21,22] Bortezomib has been proven effective in clinical trials[23] and retrospective case series,[24] and it was successfully used as adjuvant therapy after ASCT. [25] Moreover, bortezomib-containing regimens might be used as “induction therapy” prior to ASCT, rendering more subjects eligible for high-dose therapy and possibly sparing patients who achieve complete response following “induction” from having to undergo ASCT.

**Best use of novel agents**

The choice of novel agents depends upon two main determinants: 1) the phase of the disease, and 2) the type of organ involvement. Bortezomib should be used upfront in order to obtain a rapid reduction of the toxic light chain. In patients with stage 3 cardiac involvement and peripheral or autonomic neuropathy, dosage of bortezomib should be reduced (to 1–1.3 mg/m2/wk or 0.7–1 mg/m2 twice weekly).[26]

Immunomodulatory derivatives (IMiDs) thalidomide, lenalidomide (Revlimid), and pomalidomide (CC-4047, Actimid) can be used for consolidation therapy and may be considered for maintenance since they provide a durable hematologic response.[26] In patients with neuropathy, lenalidomide should be the preferred IMiD. Renal function should be closely monitored, because worsening of kidney function occurs frequently during lenalidomide therapy.[27] Prophylaxis for thromboembolism should be instituted.

**Monitoring response to therapy**

If chemotherapy succeeds in reducing the concentration of the amyloidogenic FLC and that of NT-proBNP, it significantly extends survival.[28,29] Conversely, patients for whom treatment fails to arrest progression of cardiac dysfunction as assessed by NT-proBNP and cTn have a very poor outcome.[29] Thus, hematologic and cardiac responses should be very closely monitored in AL amyloidosis (at least every 2 cycles or 3 months after transplant), in order to achieve timely initiation of second-line treatment in patients for whom first-line therapy is ineffective.

The International Society of Amyloidosis provides criteria for hematologic and cardiac response that are being updated to incorporate new evidence regarding the impact of FLC and NT-proBNP changes on survival, and these will help researchers to uniformly report results of clinical trials.[30] The French study comparing MDex and ASCT demonstrated that phase III randomized trials are feasible in patients with AL amyloidosis. National and international networks already exist that can speed up trial enrollment, while objective risk stratification based on cardiac biomarkers makes the results of clinical trials applicable to a general patient population. Phase III studies comparing MDex versus MDex with the addition of bortezomib are ongoing in Europe and in the United States, and a time will soon come when the choice of therapy for AL amyloidosis, as in other malignancies, will be supported by results of randomized trials.

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