Current treatment of AL amyloidosis

Giovanni Palladini and Giampaolo Merlini

Amyloidosis Research and Treatment Center, Biotechnology Research Laboratories, Fondazione IRCCS Policlinico San Matteo, Department of Biochemistry, University of Pavia, Italy. E-mail: gmerlini@smatteo.pv.it. *doi:10.3324/haematol.2009.008912*

Immunoglobulin light chain systemic amyloidosis (AL) is a progressive disease caused by monoclonal light chains with specific mutations that confer a unique propensity to misfold from their native structure to less stable, partially folded intermediates that self-aggregate into oligomers and then into the highly-ordered cross β-sheet structure which defines amyloid fibrils.[1] At least 11 additional proteins, synthesized by different organs (liver, intestine, etc) can cause systemic amyloidoses which can be difficult to distinguish from AL amyloidosis on a clinical basis. These proteins form amyloid deposits that share the common tinctorial, green birefringence under polarized light after staining with Congo red, and ultrastructural features, rigid, non-branching fibril with a distinct diameter of 7.5 to 10 nm (Figure 1). The unequivocal identification of the protein forming the amyloid fibril is essential for the choice of therapy.[3] A mistake in protein typing may have catastrophic therapeutic consequences, such as performing an autologous stem cell transplant in a patient with transthyretin amyloidosis who should receive a liver transplant. Proteomics technology has significantly improved the typing of amyloid deposits[2] and is routinely applied on abdominal fat aspirates at our Center.

The amyloidogenic light chains are produced by a bone marrow plasma cell clone usually of limited size, enter the circulation, and target selected organs: heart, kidney, liver, soft tissues and peripheral nervous system, trough specific, but largely undetermined, interactions with local matrix components, such as glycosaminogly-

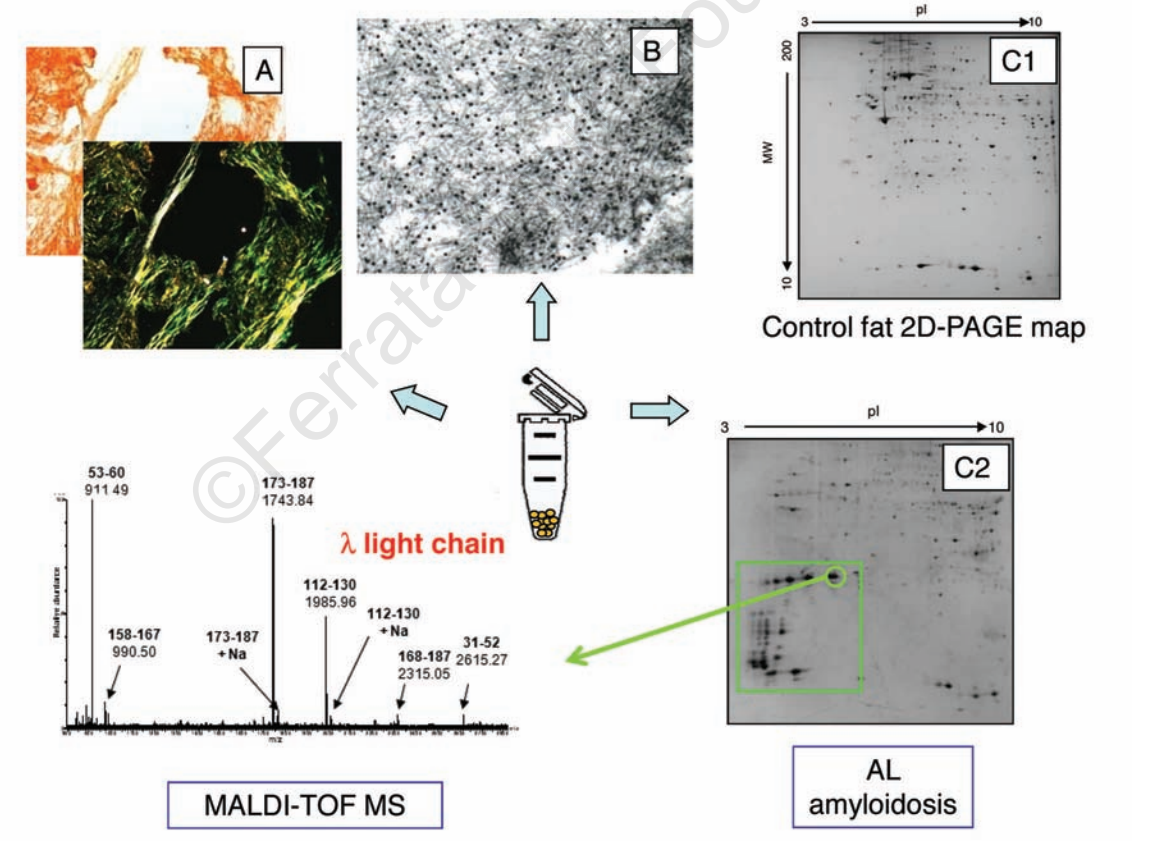

Figure 1. Typing amyloid deposits in subcutaneous adipose tissue. The 10-30 mg fine needle fat aspirate can be used for: (A) Congo red staining and analysis under polarized light showing the diagnostic green birefringence (upper left panel, Nikon Eclipse E600, magnification x 200); (B) for typing the amyloid deposits using electron-microscopy immunohistochemistry, in this case the amyloid fibrils are decorated by a gold- labeled antibody recognizing an anti-κ antibody (central upper panel, TEM Philips CM12, magnification x 22000, gold particles are 15 nm in diameter); and for proteomic analysis by bidimensional- PAGE and mass spectrometry. Comparison with control adipose tissue (C1) allowed location of prominent novel spots (squared in green) in patient (C2). Spots corresponding to fragments or post-translational modifications of the amyloidogenic protein were also observed. Identification of the novel spots, and thus amyloid typing, was obtained by MALDI-TOF mass spectrometry and peptide mass fingerprinting.

cans, and cell membrane constituents. These interactions may promote the formation of light chain oligomers which may represent the main determinant of cell toxicity and the consequent tissue dysfunction. Deposited amyloid fibrils may contribute to organ dysfunction by promoting light chain oligomerization, through increasing macromolecular crowding in the interstitial space,[4] and by damaging the tissue architecture. The aim of therapy is the prompt reduction/elimination of the supply of newly formed light chains, that feed the formation of oligomers and fibrils, in order to obtain durable improvement of AL amyloidosis-related organ dysfunction and extend survival.[5]

Several effective chemotherapy regimens have been developed during the last decade improving significantly the outlook of patients with AL amyloidosis.[6]

Current treatment of AL amyloidosis

Patients with AL amyloidosis not only have a hematologic malignancy, but also present with progressive dysfunction of one or more organs. A rapid response is essential in order to arrest the progressive organ damage and possibly rescue its function. In addition, the amyloid multiorgan involvement renders these patients particularly susceptible to the toxic effects of chemotherapy. The therapeutic armamentarium has greatly expanded in recent years from melphalan-prednisone as single resource in 1997[7] to several effective therapies including high-dose dexamethasone-based regimens[8,9] combined with melphalan (MDex),[10] thalidomide (ThalDex),[11] and cyclophosphamide-thalidomide (CTDex),[12] high-dose melphalan followed by rescue with autologous stem cell transplantation (SCT),[13,14] to the new agents, lenalidomide[15,16] and bortezomib.[17-19] MDex and SCT are the two most widely used regimens. The French Myeloma Collaborative Group compared these two regimens in a randomized trial and found no significant differences for hematologic or organ responses, and a landmark analysis, examining only patients surviving six or more months showed no survival advantage for SCT.[20] Although suboptimal patient selection for SCT may represent a limitation of this study, these results confirmed that MDex has a relevant place in the treatment of AL patients. High-dose melphalan/SCT provides a significant proportion of complete responses which translate into improved quality of life and prolonged survival.[21] However, the procedure is toxic for these fragile patients as indicated by the treatment related mortality (TRM) that in the large published series ranges from 11%[14] to 27%.[22] However, lately a careful patient selection, based also on assessment of cardiac dysfunction using biomarkers,[23,24] has significantly reduced the TRM.

Provisional suggestions for choice of chemotherapy in AL amyloidosis

Consensus criteria for best therapy have not yet been established. The choice should be based on tolerability, efficacy and rapidity of action of regimens reported to be effective. The amyloid heart involvement is by far the main prognostic determinant in AL amyloidosis.[25,26] The staging system for cardiac amyloidosis employing the biomarkers NT-proBNP[26] and troponin[27] has been validated in patients undergoing SCT.[23]

In good risk patients (younger than 65 years, with ≤2 major organs involved, NT-proBNP < 332 ng/L, cardiac troponin T < 0.035 μg/L or cardiac troponin I < 0.1 μg/L,[24] creatinine clearance ≥50 mL/min, pulmonary diffusion capacity ≥50% and systolic blood pressure > 90 mmHg) SCT with melphalan 200 mg/m^2 may be considered as front-line therapy. In our clinical practice, this group of patients represents 15% of the whole AL amyloidosis population. With the aim of reducing TRM, a risk-adapted modulation of the dose of melphalan (140–100 mg/m^2) has been proposed. However, dose reduction translated into reduced hematologic response rate (53%) with a still considerable TRM.[28] Adjuvant therapy for patients not achieving CR after SCT has been investigated. Thalidomide and dexamethasone was administered to 31 patients, improving hematologic responses in 42% of them, but was poorly tolerated.[29] In a subsequent trial, involving 27 patients, thalidomide was substituted by bortezomib and resulted in improved responses in 7/8 patients.[30]

Patients at high risk, with advanced cardiac amyloidosis, and increased troponin (cTnI >0.1 μg/L or cTnT >0.035 μg/L) and NT-proBNP (>332 ng/L), and New York Heart Association (NYHA) class III or IV or ECOG performance status ≥3 (not due to polyneuropathy), have a short median survival (3.5 months).[31] They represent approximately 20% of all our patients with AL amyloidosis. These patients are in urgent need of an effective therapy, but they are also extremely fragile and sensitive to treatment toxicity, and generally cannot tolerate high-dose dexamethasone. A gentle, rapidly-acting regimen should be preferred. We designed a study addressing specifically treatment of patients with advanced heart failure. Thalidomide was associated with melphalan and attenuated dose of dexamethasone (MTDa) in order to accelerate the response and minimize the corticosteroid toxicity. Out of the 22 patients treated, 6 died due to cardiac amyloidosis before completing cycle 3 and only 8 patients achieved a hematologic response, while 4 obtained durable improvement of cardiac dysfunction.[32] Nearly 30% of patients, particularly those who present with reduced ejection fraction at echocardiography, do not survive long enough to have a chance to respond. In these patients, heart transplantation represents the only viable alternative. In subjects with severe heart involvement but preserved ejection fraction, trials on rapidly acting regimens, such as MTDa or CTDa and, possibly, those containing low-dose (0.7-1.0 mg/m^2) bortezomib, seem warranted.

The bulk (65%) of the patients are at intermediate risk. These patients can benefit from MDex that produced 67% hematologic responses (33% CR) and 48% organ response rate. Responses to MDex resulted in a significant survival benefit and were durable, with complete remissions being maintained for more than three years in 70% of cases.[33] CTD represents a viable option and may be particularly indicated in patients who are eligible for SCT but refuse the procedure, and in those in need of a prompt response in consideration of the rapidity of action of this regimen. In this respect, bortezomib, used as single agent[19] or in combination with dexam-

ethasone[17,18] showed high response rates and a remarkable rapidity of action (median time to response less than one month).[17] The addition of bortezomib to MDex may combine the rapidity of action with the durability of response. Phase III trials are scheduled to open in the US and Europe in 2009 comparing MDex versus MDex plus bortezomib in newly diagnosed patients with AL not eligible for SCT with 200 mg/m^2 of melphalan. Relapsing and refractory patients may benefit from bortezomib[17-19] and lenalidomide[15,16] associated with dexamethasone. Whenever possible, all patients should be treated in clinical trials.

Supportive care is fundamental and aimed at maintaining quality of life, delaying organ failure and prolonging survival while specific treatment has time to take effect. Organ transplantation, particularly heart transplantation, can be offered to patients who attain CR but have irreversible organ damage, but can also represent an option to render a patient with end stage organ failure eligible for high-dose chemotherapy.

Amyloid deposits can regress if the supply of the precursor is suppressed

The first histological documentation that amyloid deposits can be reabsorbed if the synthesis of the amyloid precursor is shut down was provided by Henning, father of the great hematologist, Jan Waldenström.[34] He observed rapid resolution of hepatomegaly in a matter of a few weeks after successful surgical treatment of *lymphoid tuberculosis fistulae* with resolution of amyloid deposits at biopsy. In this case, the amyloid deposits were constituted of serum amyloid A (SAA), an acute phase protein synthesized by the liver under stimulation of the proinflammatory cytokines. In chronic tuberculosis infection, persistent high concentration of serum SAA results in formation of amyloid deposits in target organs: kidney, spleen and gastrointestinal tract.

In the present issue, the Groningen group reports the histological regression of amyloid in abdominal fat tissue in 51 patients following chemotherapy.[35] They observed a significant reduction of amyloid deposits in 80% of patients 3.2 years after achieving complete response, and no significant reabsorption in 9 patients achieving a partial response. The first consideration is that regression of AL amyloidosis is a slow process.

The molecular bases for the susceptibility of amyloid fibrils to the endogenous clearance machinery are not known but may be related to the structural organization of amyloid fibrils and their capacity to elicit a local cellular/inflammatory response. Intense research activity is ongoing aiming at targeting the amyloid deposits with innovative drugs capable of removing shielding constituents of amyloid deposits, such as serum amyloid P component (SAP)[36] and with amyloid-reactive antibodies[37] in order to promote and accelerate the reabsorption of amyloid through endogenous clearance.

Another interesting observation is that amyloid regression was not observed in the 9 patients who achieved a partial response. These patients had presented a median concentration of free light chains (FLC) that was more than eight times higher than that of complete responders (1,010 *vs.* 122 mg/L), had a more advanced disease, and the residual FLC after chemotherapy, although reduced by at least 50% by definition, was still substantial (with a median above 100 mg/L). Therefore, it is not surprising that in this small subgroup of patients, no significant regression of amyloid deposits was observed and that 7 of these patients died mostly because of amyloid progression. These data should not be interpreted such that partial response does *not* provide any clinical benefit.

A new paradigm for treatment strategy

Partial response may be a potentially misleading concept in AL amyloidosis, a disease caused by increased concentration of misfolded light chains. Clearly, the 50% reduction in concentration of FLC may have very different clinical consequences, based on the absolute concentration of residual FLC. For instance, if the starting FLC concentration is 2,000 mg/L, a residual FLC concentration of 800 mg/L, although fulfilling the criteria for partial response (60% reduction), is expected to continue to exert a substantial tissue toxicity with reduced survival. On the other hand, in a patient with a starting FLC concentration of 100 mg/L a partial hematologic response with residual FLC concentration of 40 mg/L should result in a substantial relief from light chain toxicity and, possibly, obtain a negative balance between amyloid deposition and reabsorption with prolonged survival. In larger series of patients, it has been shown that achieving a partial hematologic response translates into improved overall survival.[14,38] However, it has been reported that the percentage of FLC reduction does not predict for survival, but the absolute level of FLC achieved after SCT therapy does.[39] Ideally, one should reduce the concentration of FLC below the toxic threshold causing organ dysfunction.

Now, thanks to the availability of sensitive cardiac biomarkers it may be possible to link the extent of the hematologic response, i.e. the concentration of free light chains, to improvement of heart function.

Amyloid heart involvement is by far the most important prognostic factor since it determines the death of most of the patients,[25] and NT-proBNP[26] and troponins[27] are sensitive markers of heart damage caused by the amyloidogenic light chains. It has been observed that the reduction in FLC after therapy translates into a rapid decrease of NT-proBNP and improved survival.[40] A collaborative study performed on a total of 200 patients from the databases of the Amyloidosis centers in Pavia, Italy and London, UK who had completed one line of treatment, showed that patients who achieved a partial response associated with a decrease in NT-ProBNP have identical outcomes (survival) to the patients who achieved a complete response.[41] These data support a new paradigm in the treatment strategy of AL amyloidosis. Given that the aim of therapy is to extend the survival through the achievement of durable improvement of AL amyloidosis-related organ function, chemotherapy should be guided by frequent (every 2 cycles) assessment of FLC and cardiac biomarkers in order to optimize the benefit/toxicity ratio exposing the patients to the lowest, most effective, chemotherapy burden.

Future perspectives

Amyloidogenic plasma cells present an important distinctive feature, compared to myeloma plasma cells: they synthesize a misfolded light chain. The misfolded protein may increase the proteosomal workload and render the cells particularly vulnerable to proteasome inhibition.[42] It has been reported that the balance between proteasome workload and degradative capacity represents a critical determinant of apoptotic sensitivity of myeloma plasma cells to proteasome inhibitors.[43] Studies are now ongoing in amyloidogenic plasma cells and clarification of the molecular mechanisms of proteotoxic stress will contribute to develop targeted therapies for AL amyloidosis. The possibility of predicting the response to proteasome inhibitors,[43] allows the prompt institution of alternative treatments in patients who are unlikely to respond to this class of drugs. Furthermore, the development of new drugs targeting other components of the ubiquitin-proteasome system,[44] besides the proteasome, may offer new therapeutic opportunities, including combination therapies.

Although great advancements have been made in understanding the molecular basis of protein misfolding and fibril formation, the molecular mechanisms underlying the light chain targeting of specific tissues, such as the heart, and the consequent organ dysfunction, remain elusive. Intensive research is now focusing on this fundamental process, the identification of the molecules involved may lead to a more comprehensive treatment approach of this complex, but possibly curable disease.

Dr. Palladini is a lecturer at the University of Pavia, and an attending physician at the Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. Dr. Merlini is a professor of Clinical Biochemistry at the University of Pavia, and the director of the Amyloidosis Research and Treatment Center.

The authors' research on amyloidosis is supported by Fondazione Cariplo (Milano, Italy; Nobel Project, Transcriptomics and Proteomic Approaches to Diseases of High Sociomedical Impact: A Technology-Integrated Network), the EURAMY project (European Community's Sixth Framework Program; Ricerca Finalizzata Malattie Rare, Ministero della Salute, Istituto Superiore di Sanità (526D/63); MIUR-PRIN project 2007AE8FX2_003.

Dr. Merlini received an honorarium from Millennium Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

References

1. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med 2003;349:583-96.
2. Anesi E, Palladini G, Perfetti V, Arbustini E, Obici L, Merlini G. Therapeutic advances demand accurate typing of amyloid deposits. Am J Med 2001;111:243-4.
3. Lavatelli F, Perlman DH, Spencer B, Prokaeva T, McComb ME, Theberge R, et al. Amyloidogenic and associated proteins in systemic amyloidosis proteome of adipose tissue. Mol Cell Proteomics 2008;7:1570-83.
4. Bellotti V, Chiti F. Amyloidogenesis in its biological environment: challenging a fundamental issue in protein misfolding diseases. Curr Opin Struct Biol 2008;18:771-9.
5. Merlini G, Stone MJ. Dangerous small B-cell clones. Blood 2006;108:2520-30.
6. Merlini G, Palladini G. Amyloidosis: is a cure possible? Ann Oncol 2008;19 (Suppl 4):iv63-6.
7. Kyle RA, Gertz MA, Greipp PR, Witzig TE, Lust JA, Lacy MQ, et al. A trial of three regimens for primary amyloidosis: Colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 1997;336:1202-7.
8. Palladini G, Anesi E, Perfetti V, Obici L, Invernizzi R, Balduini C, et al. A modified high-dose dexamethasone regimen for primary systemic (AL) amyloidosis. Br J Haematol 2001;113:1044-6.
9. Dhodapkar MV, Hussein MA, Rasmussen E, Solomon A, Larson RA, Crowley JJ, et al. Clinical efficacy of high-dose dexamethasone with maintenance dexamethasone/alpha interferon in patients with primary systemic amyloidosis: results of United States Intergroup Trial Southwest Oncology Group (SWOG) S9628. Blood 2004;104:3520-6.
10. Palladini G, Perfetti V, Obici L, Caccialanza R, Semino A, Adami F, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood 2004;103:2936-8.
11. Palladini G, Perfetti V, Perlini S, Obici L, Lavatelli F, Caccialanza R, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). Blood 2005;105:2949-51.
12. Wechalekar AD, Goodman HJ, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. Blood 2007;109:457-64.
13. Skinner M, Sanchorawala V, Seldin DC, Dember LM, Falk RH, Berk JL, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 2004;140:85-93.
14. Gertz MA, Lacy MQ, Dispenzieri A, Hayman SR, Kumar SK, Leung N, et al. Effect of hematologic response on outcome of patients undergoing transplantation for primary amyloidosis: importance of achieving a complete response. Haematologica 2007;92:1415-8.
15. Dispenzieri A, Lacy MQ, Zeldenrust SR, Hayman SR, Kumar SK, Geyer SM, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood 2007;109:465-70.
16. Sanchorawala V, Wright DG, Rosenzweig M, Finn KT, Fennessey S, Zeldis JB, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood 2007;109:492-6.
17. Kastritis E, Anagnostopoulos A, Roussou M, Toumanidis S, Pamboukas C, Migkou M, et al. Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone. Haematologica 2007;92:1351-8.
18. Wechalekar AD, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD. Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease. Haematologica 2008;93:295-8.
19. Reece D, Hegenbart U, Merlini G, Palladini G, Fermand JP, Vescio RA, et al. Weekly and twice-weekly bortezomib in patients with systemic AL-amyloidosis: results of a phase 1 dose-escalation study. Blood 2009. [Epub ahead of print]
20. Jaccard A, Moreau P, Leblond V, Leleu X, Benboubker L, Hermine O, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med 2007;357:1083-93.
21. Sanchorawala V, Skinner M, Quillen K, Finn KT, Doros G, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. Blood 2007;110:3561-3.
22. Vesole DH, Perez WS, Akasheh M, Boudreau C, Reece DE, Bredeson CN. High-dose therapy and autologous hematopoietic stem cell transplantation for patients with primary systemic amyloidosis: a Center for International Blood and Marrow Transplant Research Study. Mayo Clin Proc 2006;81:880-8.
23. Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, et al. Prognostication of survival using cardiac troponins and N-terminal pro-brain natriuretic peptide in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. Blood 2004;104:1881-7.
24. Gertz M, Lacy M, Dispenzieri A, Hayman S, Kumar S, Buadi F, et al. Troponin T level as an exclusion criterion for

stem cell transplantation in light-chain amyloidosis. Leuk Lymphoma 2008;49:36-41.
25. Obici L, Perfetti V, Palladini G, Moratti R, Merlini G. Clinical aspects of systemic amyloid diseases. Biochim Biophys Acta 2005;1753:11-22.
26. Palladini G, Campana C, Klersy C, Balduini A, Vadacca G, Perfetti V, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. Circulation 2003;107:2440-5.
27. Dispenzieri A, Kyle RA, Gertz MA, Therneau TM, Miller WL, Chandrasekaran K, et al. Survival in patients with primary systemic amyloidosis and raised serum cardiac troponins. Lancet 2003;361:1787-9.
28. Gertz MA, Lacy MQ, Dispenzieri A, Ansell SM, Elliott MA, Gastineau DA, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. Bone Marrow Transplant 2004;34:1025-31.
29. Cohen AD, Zhou P, Chou J, Teruya-Feldstein J, Reich L, Hassoun H, et al. Risk-adapted autologous stem cell transplantation with adjuvant dexamethasone +/- thalidomide for systemic light-chain amyloidosis: results of a phase II trial. Br J Haematol 2007;139:224-33.
30. Landau HJ, Hoffman J, Hassoun H, Elizabeth H, Riedel E, Nimer SD, et al. Adjuvant bortezomib and dexamethasone following risk-adapted melphalan and stem cell transplant in patients with light-chain amyloidosis (AL). J Clin Oncol 2009;27:15s[Abstract 8540].
31. Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol 2004;22:3751-7.
32. Palladini G, Russo P, Lavatelli F, Nuvolone M, Albertini R, Bosoni T, et al. Treatment of patients with advanced cardiac AL amyloidosis with oral melphalan, dexamethasone, and thalidomide. Ann Hematol 2009;88:347-50.
33. Palladini G, Russo P, Nuvolone M, Lavatelli F, Perfetti V, Obici L, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. Blood 2007;110:787-8.
34. Waldenstrom H. On the formation and disappearance of amyloid in man. Acta Chir Scand 1928;63:479-530.
35. Van Gameren I, et van Rijswijk MH, Bijzet J, Vellenga E, Hazenberg BF. Histological regression of amyloid in AL amyloidosis is exclusively seen after normalization of serum free light chain. Haematologica 2009;94:1094-100.
36. Pepys MB, Herbert J, Hutchinson WL, Tennent GA, Lachmann HJ, Gallimore JR, et al. Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. Nature 2002;417:254-9.
37. Hrncic R, Wall J, Wolfenbarger DA, Murphy CL, Schell M, Weiss DT, et al. Antibody-mediated resolution of light chain-associated amyloid deposits. Am J Pathol 2000;157:1239-46.
38. Lachmann HJ, Gallimore R, Gillmore JD, Carr-Smith HD, Bradwell AR, Pepys MB, et al. Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. Br J Haematol 2003;122:78-84.
39. Dispenzieri A, Lacy MQ, Katzmann JA, Rajkumar SV, Abraham RS, Hayman SR, et al. Absolute values of immunoglobulin free light chains are prognostic in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. Blood 2006;107:3378-83.
40. Palladini G, Lavatelli F, Russo P, Perlini S, Perfetti V, Bosoni T, et al. Circulating amyloidogenic free light chains and serum N-terminal natriuretic peptide type B decrease simultaneously in association with improvement of survival in AL. Blood 2006;107:3854-8.
41. Wechalekar A, Merlini G, Gillmore JD, Russo P, Lachmann HJ, Obici L, et al. Role of NT-ProBNP to assess the adequacy of treatment response in AL amyloidosis. Blood 2008;112:596-7.
42. Sitia R, Palladini G, Merlini G. Bortezomib in the treatment of AL amyloidosis: targeted therapy? Haematologica 2007;92:1302-7.
43. Bianchi G, Oliva L, Cascio P, Pengo N, Fontana F, Cerruti F, et al. The proteasome load versus capacity balance determines apoptotic sensitivity of multiple myeloma cells to proteasome inhibition. Blood 2009;113:3040-9.
44. Soucy TA, Smith PG, Milhollen MA, Berger AJ, Gavin JM, Adhikari S, et al. An inhibitor of NEDD8- activating enzyme as a new approach to treat cancer. Nature 2009;458:732-6.