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Light chain amyloidosis: the heart of the problem

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In this issue of Haematologica, Dinner *et al.* report the outcome of a pilot study of an oral regimen of lenalidomide in combination with dexamethasone and low-dose melphalan in 25 patients with light chain amyloidosis (AL), most of them with cardiac involvement.[1] The treatment proved to be toxic and unable to improve survival in patients with advanced amyloid cardiomyopathy and poor performance status. High rates of early cardiac deaths (42%) and of cardiac arrhythmias (33%), probably triggered by high-dose dexamethasone, drug myelotoxicity limiting the duration of treatment to 3 cycles, and a mere 9% cardiac response rate, contributed to a highly disappointing median overall survival of 1.75 months in patients with late-stage heart damage. The outcome of this study highlights the urgent need for novel approaches in order to improve the prospects of AL amyloidosis patients with advanced cardiomyopathy.

Light chain amyloidosis is the most common systemic amyloidosis, with an incidence of 10 patients per million per year, resulting in approximately 5,000 new patients/year in the European Union. It is sustained by a usually small, indolent, plasma cell clone whose biological features, shared by less proliferative plasma cell dyscrasias, make it more sensitive to chemotherapy. The clonal plasma cells synthesize an excess of light chains (LC) with specific mutations and unique structural features causing systemic proteotoxicity. Interactions of the misfolded LCs with cells, extracellular matrix components and other constituents commonly found in amyloid deposits, such as serum amyloid P (SAP), and other molecules, play an important role in the disease process and are potential targets for therapy. AL amyloidosis is also the most severe systemic amyloidosis because over 70% of patients present with cardiac involvement, which results in the development of rapidly progres-

Table 1. Studies on front-line treatment of patients with AL amyloidosis and advanced cardiac involvement.

Author	Regimens and dosing schedule	N.	Cardiac biomarkers / staging	NYHA class III or IV	HR/CR	CaR	Day 100 mortality	Median overall survival
Lebovic, *et al.*[26]	MDex M 0.11-0.22 mg/Kg on Days 1-4 Dex 20 mg/m^2 on Days 1-4	40	Median cTnI 0.12 ng/mL Median BNP 1000 ng/L	85% class II or higher	58% / 13%	-	23%	10.5 months
Palladini, *et al.*[27]	MTDex M 0.22 mg/Kg T 100 mg/Day Dex 20 mg on Days 1-4	22	Stage III: 73% Median NT-proBNP 11282 ng/L	100%	36% / 4%	18%	27%	5.3 months
Dietrich, *et al.*[28]	Intravenous MDex M 16 mg/m^2 on Day 1 Dex 40 mg on Days 1-4	61	Stage III: 53% Median NT-proBNP 4420 ng/L	64%	44% / 11%	14%	33% died on treatment	17.5 months
Wechalekar, *et al.*[12]	MDex T combinations B combinations L combinations	154 96 23 13	Stage III: 100% Median NT-proBNP 9106 ng/L NT-proBNP >8500 ng/L in 52%	52%	40% / 15% 32% / 11% 43% / 26% 38% / 0%	12%	30%	7.1 months (in patients with NT-proBNP >8500 ng/L the median OS is 4.6 months)
Dinner, *et al.*[1]	MLDex M 0.18 mg/Kg on Days 1-4 L 10 mg on Days 1-21 Dex 40 mg/week	25	Stage III: 36% Median NT-proBNP 2443 ng/L	20%	58% / 8%	9%	40%	58% at 12 months (1.8 months in stage III)

Only studies on front-line therapy including at least one-third of stage III patients are listed. B: bortezomib; BNP: natriuretic peptide type-B; CaR: cardiac response; CR: complete response; Dex: dexamethasone; HR: hematologic response; L: lenalidomide; M: melphalan; N: patients' number; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-natriuretic peptide type-B; OS: overall survival; T: thalidomide.

sive heart failure, ventricular arrhythmias and over 50% mortality within one year.[2] The incidence of cardiac involvement continues to rise, owing to increasingly effective detection.[3] Advanced echocardiographic techniques, such as tissue Doppler and strain imaging, allow the identification of early, subtle changes and provide prognostic information. Cardiac magnetic resonance proves useful in diagnosing and possibly monitoring amyloid deposits. Cardiac scintigraphy with bone tracers helps differentiate AL from non-AL (hereditary, senile) amyloidosis.

The molecular mechanisms involved in amyloid cardiac damage are the subject of intensive investigation. A substantial body of experimental evidence has recently altered the hypothesis underlying the etiology of AL cardiomyopathy, shifting it from a disease of simple passive amyloid infiltration to one in which the direct cardiotoxic effects of amyloidogenic LC proteins play a critical role. Previous and recent research have demonstrated that AL-LC precursor proteins, independent of cardiac fibril formation and passive restriction of cardiac function, trigger a direct cardiotoxic response causing impaired cardiomyocyte function *in vitro*.[4,5] More recently, it has been shown that injection of amyloid LC causes cardiac dysfunction and early death in zebrafish.[6] The toxic effect of the LC described in these model systems is supported by clinical observations that cardiac stress, as measured by circulating levels of type B natriuretic peptides (BNP or NT-proBNP) may be reduced in parallel with the reduction in free LC (FLC) levels following chemotherapy and such reductions translate in improved survival.[7] The extent of cardiac damage, staged using the cardiac biomarkers NT-proBNP and troponins[8] is a powerful predictor of survival, and the burden of the amyloid LC also has a significant impact on outcome.[9] It is, therefore, vital to promptly reduce the concentration of cardiotoxic LCs.

Two studies reported the use of the same oral regimen of lenalidomide in combination with dexamethasone and melphalan described in the current study by Dinner *et al.*[1] Moreau *et al.*, in 26 patients (12 of whom were in cardiac stage II or III), reported a 58% hematologic response rate, with 40% cardiac response, and 81% survival at two years.[10] Sanchorawala *et al.* reported a 44% hematologic response rate (no cardiac response) with significant toxicity and a 19% mortality in the first three months in a series including 69% of patients with heart involvement, 81% of whom were in cardiac stage II and III.[11] These discordant outcomes depend on the variable percentage and severity of cardiac involvement in the patient populations. A recent European collaborative study analyzed treatment outcomes of 346 patients with cardiac stage III AL amyloidosis from the United Kingdom, Italy, Germany and Greece.[12] The results show that cardiac stage III AL amyloidosis is actually a heterogeneous disease, comprising both patients with less advanced cardiac damage, in whom response to therapy conferred survival improvement dependent on the depth of hematologic response, and patients with severe amyloid cardiomyopathy (characterized by extreme elevation of NT-proBNP above 8500 ng/L and systolic blood pressure <100 mm Hg) who die within a few weeks. Several studies evaluated the efficacy of front-line conventional and novel therapies in patients with amyloid cardiomyopathy. However, most of them were retrospective and some were performed before cardiac risk stratification was available, making them hardly comparable and prevented solid conclusions being drawn. Thus, we focused our analysis on the studies reporting cardiac staging and including only patients treated frontline (Table 1). The outcome of these studies is invariably dismal, with 20-40% early mortality rates, median survival ranging from 5 to 17 months depending on the proportion of patients with severe heart failure. The overall

response rates seem almost unaffected by the addition of novel agents, although bortezomib combinations probably give a higher rate of complete response that may translate into better cardiac outcome.[12] Improvement of cardiac function is infrequent, being observed in less than 20% of cases. Collectively these data indicate that current therapy for patients with amyloid cardiomyopathy is largely unsatisfactory and calls for better approaches. As reported in the European collaborative study, patients with less advanced cardiac damage tolerate chemotherapy better and are significantly more likely to respond to treatment.[12] In addition, patients with early heart involvement and only moderately elevated cardiac biomarkers (NT-proBNP < 5000 ng/L and troponin T < 0.06 μg/L) can safely undergo autologous stem cell transplantation (ASCT)[13] with satisfactory outcomes.[14] These findings highlight the critical importance of early detection of amyloid cardiomyopathy. Furthermore, although the survival of patients with AL amyloidosis has been significantly improved over the last two decades by effective regimens and novel agents,[15,16] the 25-30% rate of early deaths (within one year of diagnosis), almost invariably cardiac, still represents the major impediment for further improvements in survival. Investigators involved in the care of patients with AL amyloidosis have deployed several lines of intervention to tackle this vital problem.

A) *Early diagnosis*. The cardiac biomarker NT-proBNP has 100% sensitivity in detecting amyloid cardiac involvement, anticipating echocardiographic abnormalities and preceding the onset of cardiac symptoms by several months.[17] The great majority of patients with amyloid cardiomyopathy have an abnormal FLC κ/λ ratio. Therefore, we have recently proposed routine adoption of a simple strategy, i.e. checking NT-proBNP levels during monitoring of patients with monoclonal gammopathy of undetermined significance with abnormal κ/λ ratio, in order to detect heart involvement at a very early stage.[18] Increasing knowledge and awareness of these rare diseases, through national and international collaborative networks and patients' associations, is also fundamental for improving early recognition of these rapidly progressive diseases in which 'time' is 'life'.

B) *Synergize treatment and improve tolerability*. Several lines of evidence indicate that a profound and early reduction of cardiotoxic LC is critical to improving survival. Achieving this aim remains difficult in these frail patients extremely sensitive to the toxicity of therapy. A possible strategy would be to combine agents with synergistic mechanisms of action, thereby allowing lower doses of each individual agent to be used, thus improving tolerance while producing rapid and deep responses.[12] Recently, an over 90% survival at two years was reported in a retrospective series in 20 stage III patients receiving cyclophosphamide, bortezomib and dexamethasone. However, this study also included previously treated subjects.[19] Prospective trials of regimens based on rapidly acting proteasome inhibitors in association with alkylating agents and low-dose dexamethasone in stage III patients are ongoing to validate this strategy. Silencing the amyloid LC isotype gene could be an alternative and less toxic strategy.[20]

C) *Accelerate recovery of cardiac function*. The most advanced stage III patients, with extreme elevations of NT-proBNP and hypotension, pose an extremely difficult challenge. These very ill patients cannot withstand even attenuated regimens and achieving good quality response (≥ VGPR) may not be sufficient to rescue heart function.[12] Strategies directed at promoting the resorption of amyloid deposits, such as immunotherapy[21] or small molecules like doxycycline[22] in combination with effective, attenuated chemotherapy, could potentially accelerate the recovery of cardiac function, improving the quality of life and extending survival. Drugs counteracting the proteotoxicity of the amyloid light chains, such as epigallocatechin-gallate,[23] can also improve heart performance. Several trials are ongoing to test these novel strategies.

D) *Supporting cardiac function.* Careful control of body weight and judicious diuretic use are fundamental. Devices that assist ventricular function have been used in patients with terminally compromised cardiac function, with disappointing results, mostly due to high morbidity.[24] Cardiac transplantation represents a life-saving approach, particularly in young patients without significant extra-cardiac organ involvement. Sequential ASCT can warrant extended survival and quality of life.[25] However, the feasibility of this approach is limited by the availability of organ donors.

Reduction of morbidity and mortality in patients with cardiac AL amyloidosis requires the development of innovative and more effective remedies. Basic research into the molecular mechanisms involved in cardiac injury caused by amyloid proteins is essential to direct therapeutic efforts. In the near future, new treatment options targeting multiple steps in the process of amyloidogenesis, from reducing the amyloid precursor protein to accelerating the clearance of amyloid deposits and counteracting proteotoxicity, have the potential to improve clinical efficacy while reducing treatment-related complications.

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Pathogen safety of long-term treatments for bleeding disorders: still relevant to current practice

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Hemophilia defines a group of hereditary bleeding disorders: hemophilia A (deficiency of Factor VIII, FVIII), hemophilia B (deficiency of FIX), and parahemophilia (deficiency of FV). These result from mutations in clotting factor genes. As in the large majority of bleeding disorders (Table 1), replacement of deficient coagulation factor protein is required to prevent or reverse acute bleeding episodes. This is achieved by the administration of recombinant or plasma-derived clotting factor concentrates (PDCFC), e.g. FVIII or FIX; or inhibitor-bypassing agents such as rFVIIa or Factor VIII inhibitor bypass activity (FEIBA). Being effective at preventing and treating bleeding in patients with hemophilia, and enabling self-administration at home, PDCFC has replaced cryoprecipitate and