Is there still a place for autologous stem cell transplantation in systemic AL amyloidosis with severe renal disease?

Frank Bridoux¹, Vincent Javaugue¹, Jean Paul Fermand² and Arnaud Jaccard³

¹Department of Nephrology, Dialysis and Renal Transplantation, University Hospital of Poitiers, Centre de référence de l’amylose AL et des autres maladies par dépôts d’immunoglobuline monoclonale, Poitiers, France. ²Department of Hematology and Clinical Immunology, Saint Louis University Hospital, Paris, France and ³Department of Hematology, University Hospital of Limoges, Centre de référence de l’amylose AL et des autres maladies par dépôts d’immunoglobuline monoclonale, Limoges, France

Correspondence and offprint requests to: Frank Bridoux; E-mail: f.bridoux@chu-poitiers.fr; Frank.BRIDOUX@chu-poitiers.fr

In this issue, Leung et al. [1] retrospectively studied the Mayo Clinic cohort of patients treated with high-dose melphalan followed by autologous stem cell transplantation (HD/M/ASCT) for systemic immunoglobulin light chain (AL) amyloidosis. They show that renal failure requiring dialysis within 30 days of HD/M/ASCT is associated with high treatment-related mortality (TRM), indicating that despite spectacular advances in the treatment of AL amyloidosis, management of the more fragile patients remains challenging.

Since most patients have an underlying small B-cell clone and predominant renal symptoms, systemic AL amyloidosis belongs to the spectrum of monoclonal gammopathy of renal significance [2, 3]. Widespread deposition of monoclonal light chains (LCs) that aggregate into insoluble fibrils is responsible for a wide range of symptoms, related to modification of the structure of involved organs and cellular toxicity of amyloidogenic LCs [4]. Without treatment, median overall survival is 12 months and <6 months in patients with symptomatic heart disease at diagnosis [5, 6]. Accumulation of amyloid fibrils depends on the rate of production of the precursor and on catabolism of deposited fibrils. The later process is slow, due to fibril binding to serum amyloid P component (SAP), a protein of the pentraxin family that stabilizes aggregates and prevents their proteolytic degradation by macrophages. Recently, depletion of serum SAP with CHPHC ((R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid), followed by the injection of a monoclonal anti-SAP antibody, was shown to effectively accelerate the elimination of amyloid through opsonization of deposits and complement activation [7]. A recent Phase II study showed encouraging results in patients with systemic amyloidosis and liver involvement [8]. Two other monoclonal antibodies targeting a conformational epitope on amyloid fibrils or amyloid precursor oligomers are under evaluation, one in an ongoing Phase III study in AL patients with heart involvement (EudraCT: 2014-003865-11). Until the demonstration of the safety and efficacy of novel immunotherapeutic approaches, treatment of systemic AL amyloidosis remains based on the suppression of clonal plasma cells secreting amyloidogenic free LCs (FLCs).

Due to the slow clearance of deposited fibrils, organ responses are often delayed and cannot serve as indicators of treatment efficacy. The goal of chemotherapy is to rapidly obtain deep and sustained suppression of FLCs, as time to response and quality of haematological response strongly affect patient survival [3, 9–11]. Haematological response is based on FLC levels, which should be measured at diagnosis and monitored regularly throughout treatment. According to current international criteria, partial haematological response is defined by a reduction of at least 50% in the difference between the concentration of the involved (most commonly λ) and the non-involved isotype (dFLC), whereas very good partial response is defined by post-treatment dFLC ≤40 mg/L, and complete response (CR) by normal κ over λ ratio with negative serum immunofixation [11–13].

Early diagnosis and careful evaluation of heart involvement is crucial for the choice of treatment. More than 60% of patients present with heart disease, a prevalence close to that of renal involvement. Amyloid hypertrophic cardiomyopathy is characterized by early diastolic dysfunction that rapidly progresses towards intractable cardiac failure without appropriate therapy. Arrhythmia or conduction blocks account for >50% of deaths [5, 14]. Current diagnostic criteria require the association of a ≥12-mm diastolic septum thickness with suggestive electrocardiographic changes, particularly microvoltages in standard derivations [12, 13]. The initial workup should include systematic measurement of biomarkers troponin T and NT-proBNP to assess the severity of heart disease. Cardiac magnetic resonance imaging and Doppler echocardiography are also useful to detect early signs of cardiac involvement, such as abnormal longitudinal deformation (2D-strain) [14]. The Mayo Clinic staging system is widely used to guide management. Patients are

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classified with Stage I, II or III disease, if they have none, one or both of the following findings: NT-proBNP ≥332 ng/L and troponin T ≥0.035 µg/L. Mayo Clinic stage is strongly associated with overall survival, Stage III patients bearing the worse prognosis [11, 15, 16].

For years, the cornerstone of treatment was conventional oral low-dose melphalan and prednisone. This regimen, by inducing a low haematological response rate of 30%, often delayed, resulted in a modest 6-month increase in patient survival [5, 6]. As recalled by Leung et al. [1], the first effective treatment strategy in AL was HDM/ASCT, which allowed a dramatic increase in haematological responses and overall survival. However, it soon appeared that HDM/ASCT could be offered only to selected patients, because of an unacceptable TRM (i.e. within the first 3 months) in older patients, and those with disseminated organ involvement or severe cardiac disease. TRM rates as high as 40% were reported when HDM/ASCT was performed outside specialized centres without careful patient selection [17]. The introduction of eligibility criteria for HDM/ASCT led to significant reduction in TRM, currently <10% in expert centres [18–20]. Consensus recommendations are to offer HDM/ASCT only to patients aged ≤70 years, with up to two organs involved, in the absence of severe heart, renal or liver involvement [21, 22]. In their study, Leung et al. identified acute kidney injury with need for dialysis therapy within 30 days of HDM/ASCT as a strong predictive factor of TRM [1]. TRM was 44% in patients who required dialysis during the peri-transplant period, and <7% in the remaining patients. In multivariate analysis, baseline serum creatinine >1.7 mg/dL and hypoalbuminaemia <2.5 g/dL were independently associated with starting of dialysis in the peri-transplant period, suggesting that both conditions should be regarded as criteria of non-eligibility for HDM/ASCT.

This study is important, not only because it refines the indications of high-dose therapy but also because it questions its place in the therapeutic management of systemic AL amyloidosis. A study from the Mayo Clinic in 2001 showed that if strict eligibility criteria for HDM/ASCT were applied to AL patients, only 16% were candidates. Moreover, 24-month survival in highly selected patients treated with conventional chemotherapy was similar to that of patients undergoing HDM/ASCT.
As stressed by Leung et al. [1], since significant heart disease is the major criteria for non-eligibility, most candidates for HDM/ASCT have predominant renal involvement. If nephrotic syndrome and impaired renal function become additional exclusion criteria, the proportion of eligible patients is likely to decrease significantly. Moreover, the efficacy and safety of HDM/ASCT compared with standard-dose chemotherapy are still debated. Indeed, despite strict patient selection, HDM/ASCT is still associated with TRM of ~5% [20]. Moreover, in 2007, a randomized controlled trial did not show any superiority of HDM/ASCT over conventional chemotherapy with melphalan plus dexamethasone (M-Dex). The median overall survival was significantly longer in patients treated with M-Dex compared with those assigned to receive HDM/ASCT. A subgroup analysis of high-risk patients showed similar overall survival, and no significant difference was observed in low-risk patients who had received therapy at 3 years [24]. M-Dex is a cost-effective option as first-line treatment, allowing haematological response in nearly 65% of patients, and CR in 20%. The tolerance profile is good, with a low risk of myelodysplasia or acute leukaemia. Since 2007, M-Dex has been widely used as a first-line therapy, particularly in Europe. However, it rapidly became evident that other strategies were required in patients with advanced heart involvement (Mayo Clinic Stage III), whose survival remained poor. The introduction of novel anti-myeloma agents, including the immunomodulatory drugs thalidomide and lenalidomide, or the proteasome inhibitor bortezomib, recently opened novel perspectives. Particularly, combinations of bortezomib and dexamethasone with an alkylating agent, melphalan (BM-Dex regimen) or cyclophosphamide (VCD regimen) are associated with haematological response rates of ≥80%, with >50% of CR [25–27]. The safety and efficacy of BM-Dex compared with M-Dex is currently evaluated in an international randomized trial. Some centres, including ours, have developed risk-adapted treatment strategies based on conventional chemotherapy (Figure 1) that result in overall survival similar to that reported with HDM/ASCT in selected patients [28–31]. The use of bortezomib as front line in Stage III patients, or after insufficient FLC response, is controversial. However, even with bortezomib-based combinations, survival remains notably poor in Stage III patients with NT-proBNP level >8500 ng/L, in whom cardiac transplantation is the only life-saving option [27, 30, 31]. In their conclusion Leung et al. [1] suggest that the benefit–risk ratio of HDM/ASCT is clearly unfavourable in severe renal patients, who bear an excessive risk of TRM. This recommendation is wise, because safer and effective options are available for these patients, such as the VCD regimen, which does not require dose adjustment to renal function [3, 25–27].

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Leung et al. The impact of dialysis on the survival of patients with immunoglobulin light chain (AL) amyloidosis undergoing autologous stem cell transplantation. Nephrol Dial Transplant 2016; 31: 1284–1289)

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Received for publication: 16.12.2015; Accepted in revised form: 22.12.2015