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Therapies for cardiac light chain amyloidosis: An update

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ABSTRACT

Light-chain (AL) amyloidosis is the most common type of systemic amyloidosis, affecting around 10 people per million per year. This serious disorder is characterized by the presence of a clone of bone marrow plasma cells that produces monoclonal light chains (LCs) of the κ or predominantly λ type. These amyloidogenic LCs undergo extracellular misfolding and aggregation into proteotoxic soluble oligomers and amyloid fibrils that deposit within tissues. The lethal consequences of AL amyloidosis are due to the toxic products (the LCs) and not to the malignant behaviour of the plasma cell clone. Almost 80% of patients with AL amyloidosis have some degree of cardiac involvement, manifesting as heart failure (HF), and carrying a particularly poor prognosis.

The past decade has seen major advances in the treatment of AL amyloidosis, and a rapidly fatal disease has become a treatable and possibly curable condition. The number of therapeutic options is rapidly expanding, offering hope to address currently unmet needs (most notably, the treatment of frail patients). The treatment of AL amyloidosis consists in a combination of agents targeting multiple steps of the amyloid cascade, associated with effective HF management, and there is ground for hope for dramatically improving the outcome in the near future.

In the present review we will summarize our current knowledge on therapy for cardiac AL amyloidosis, targeting clinical cardiologists involved in the care of this serious disorder.

1. Introduction

Light-chain (AL) amyloidosis is the most common type of systemic amyloidosis [1], affecting around 10 people per million per year, approximately 5000 new patients in the European Union [2,3]. This often fatal disorder is characterized by the presence of a clone of bone marrow plasma cells that produces monoclonal light chains (LCs) of the κ or predominantly λ type [2]. These amyloidogenic LCs undergo extracellular misfolding and aggregation into proteotoxic soluble oligomers and amyloid fibrils that deposit within tissues. The lethal consequences of AL amyloidosis are due to the toxic products (the LCs), and not to the malignant behaviour of the plasma cell clone [2]. The clinical presentation is heterogeneous depending on organ involvement (most commonly heart and kidney, gastrointestinal tract, autonomous or peripheral nervous system and soft tissues) [4].

Almost 80% of patients with AL amyloidosis have some degree of cardiac involvement, manifesting as heart failure (HF), and carrying a particularly poor prognosis [2,5]. Indeed, when categorizing patients with AL amyloidosis according to N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP; cut-off 332 ng/L) and cardiac troponin I (cTnI; cut-off 100 ng/L), survival progressively decreased from stage I (both biomarkers below cut-offs) to stage II (only one biomarker increased), and to stage III (both biomarkers increased); patients with stage IIIb (NT-proBNP > 8500 ng/L, 20% of patients) had a dismal prognosis, with median survival between 4 and 7 months [6–8]. Cardiac involvement at baseline is a major determinant of survival, and *cardiac response to treatment* (*defined* as >30% and >300 ng/L decrease in NT-proBNP when baseline NT-proBNP is ≥650 ng/L) [9] is a powerful predictor of prognosis. With regard to the hematologic response, it can be classified as complete response (normal free LC - FLC - ratio

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and negative serum and urine immunofixation), very good partial response (difference between involved and uninvolved FLCs - dFLC < 40 mg/L), partial response (dFLC decrease > 50%), and no response [9]. Hematologic and cardiac responses predict survival as early as 3 months after treatment initiation [9].

Therapeutic goals in cardiac AL amyloidosis are rapid elimination of the amyloid precursor, removal of fibrils, and effective management of HF (Fig. 1). The research on this field is rapidly expanding, and many drugs and regimens have been proposed over the last years. In the present review we will summarize our current knowledge on therapy for cardiac AL amyloidosis, targeting clinical cardiologists involved in the care of this serious disorder, as well as cardiologists with expertise in heart failure or cardio-oncology.

2. Therapies targeting the plasma cells: at the root of the problem

Chemotherapy targeting the underlying plasma cell dyscrasia has changed considerably in the past decade, with markedly improved response rates and prolonged survival. Since AL amyloidosis is a rare disease, treatment recommendations rely mostly on phase 2 studies or retrospective analyses, and only a few randomized phase 3 studies have been carried out [10,11]. Chemotherapy for AL amyloidosis is based on regimens used for the treatment of multiple myeloma (MM), with adaptations in terms of dose and schedule [12].

High-dose melphalan (HDM) with autologous stem cell transplantation (*ASCT*) was introduced in the care of AL amyloidosis by the Boston Group [13], and is now considered the treatment of choice for approximately 20% of patients with good functional status without severe cardiac and renal involvement [14]. Indeed, ASCT is the most cytotoxic therapy against plasma cells, resulting in high response rates and the potential to avoid ongoing chemotherapy [14]. Careful selection of candidates to ASCT, especially with regard to cardiac involvement, is mandatory because of the high transplant-related mortality. A prospective, randomized, phase 3 trial comparing oral melphalan plus dexamethasone (MDex) *vs.* HDM with ASCT did not show a superiority of ASCT [14]. In a retrospective, multicentre analysis of 1536 patients with AL amyloidosis undergoing ASCT from 1995 to 2012, mortality at 30 and 100 days declined progressively, and overall survival improved [15]. Currently, a hematological response is achievable in >70% of patients, and complete response in approximately 30 to 40% [16]. The reported 10-year survival is about 40% [17,18]. When this therapeutic approach is chosen, close cardiologic evaluation is essential because stem cell collection is often associated with fluid retention and hypotension, and atrial arrhythmias may occur following chemotherapy [19]. Furthermore, even steroid treatment may promote fluid retention, as well as requiring careful titration. In general, it has been recommended that cardiologists with expertise in AL amyloidosis are involved during the chemotherapy treatment, and visit patients at frequent intervals throughout chemotherapy to adjust concomitant medications [19].

Oral MDex is a very effective and well tolerated regimen that for several years has been the standard of care for patients not eligible to ASCT [20]. A recent update of the outcome of this regimen showed an overall median survival of 7.4 years [21]. The hematologic response rate was 76%, with 31% of patients obtaining complete response, with 37% cardiac response and 24% kidney response, thus confirming the efficacy of this regimen [21].

The degradation of cellular proteins is a tightly regulated and complex process that plays a central role in regulating cellular function and maintaining homoeostasis in every eukaryotic cell [22]. The ubiquitin-proteasome pathway represents the major pathway for intracellular protein degradation [22]. >80% of cellular proteins are degraded through this pathway, including those involved in the regulation of numerous cellular and physiological functions, such as cell cycle, apoptosis, transcription, DNA repair, protein quality control and antigens [22]. *Proteasome inhibitors* (*PIs*) block the proteasome either reversibly or irreversibly, causing downstream effects that can be summarized as follows: upregulation of proapoptotic protein expression, downregulation of several apoptosis inhibitors and proteins involved in DNA repair and activation of the unfolded protein response [23]. PIs also affect cell microenvironment, including inhibition of cytokine secretion, suppression of adhesion molecule expression and inhibition of angiogenesis [23].

The introduction of proteasome inhibitors has represented a major breakthrough in the care of AL amyloidosis. Bortezomib is a reversible

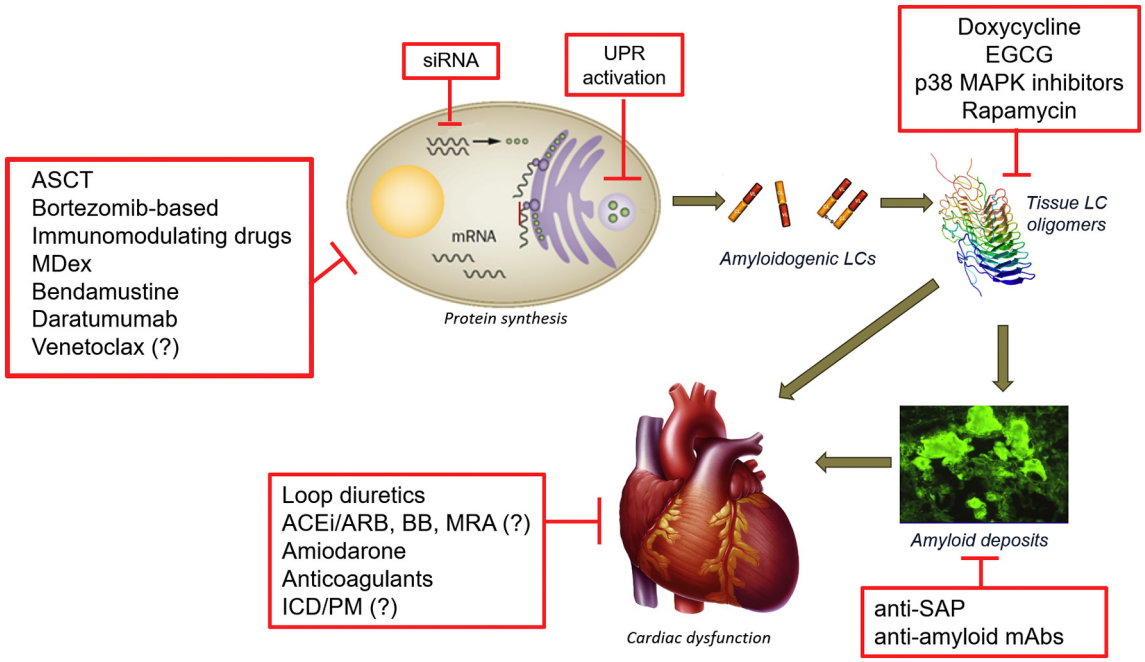

Fig. 1. Targets for treatment in cardiac light-chain (AL) amyloidosis, and possible approaches. The therapeutic approaches are discussed extensively in the text. ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ASCT, autologous stem cell transplantation; BB, beta-blocker; EGCG, epigallocatechin-3-gallate; HF, heart failure; ICD, implantable cardioverter defibrillator; LCs, light chains; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MRA, mineralocorticoid receptor antagonist; PM, pacemaker; SAP, serum amyloid P component; siRNA, small interfering RNAs; UPR, unfolded protein response.