European Journal of Cancer 76 (2017) 183–187

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Current Perspective

Sequential cyclophosphamide-bortezomib-dexamethasone unmasks the harmful cardiac effect of dexamethasone in primary light-chain cardiac amyloidosis

Fabien Le Bras [a,b,c,1], Valerie Molinier-Frenkel [b,c,d,1], Aziz Guellich [b,c,e,f], Jehan Dupuis [a,c], Karim Belhadj [a,c], Soulef Guendouz [b,c,e,f], Karima Ayad [b,c,e,f], Magali Colombat [g], Nicole Benhaiem [h], Claire Marie Tissot [b,c,e,f], Anne Hulin [i], Arnaud Jaccard [j], Thibaud Damy [b,c,e,f,k,*]

[a] *Lymphoid Malignancies Unit, Henri Mondor Hospital, Créteil, France*
[b] *Paris XII University, UPEC, Créteil, France*
[c] *GRC Amyloid Research Institute, IMRB-INSERM U955, and Mondor Amyloidosis Network, Créteil, France*
[d] *Department of Clinical Immunology, AP-HP, Henri-Mondor Hospital, Créteil, France*
[e] *Department of Cardiology, AP-HP, Henri-Mondor Hospital, Créteil, France*
[f] *DHU ATVB, Créteil, France*
[g] *Paris Descartes University, Proteomics Platform, Paris, France*
[h] *Department of Pathology, AP-HP, Henri-Mondor Hospital, Créteil, France*
[i] *Laboratory of Pharmacology, AP-HP, Henri-Mondor Hospital, Créteil, France*
[j] *Department of Hematology, University Hospital of Limoges, Centre de référence de l'amylose AL et des autres maladies par dépôts d'immunoglobuline monoclonale, Limoges, France*
[k] *Inserm Clinical Investigation Center 1430, Créteil, F-94000, France*

Received 4 December 2016; received in revised form 2 February 2017; accepted 4 February 2017
Available online 20 March 2017

KEYWORDS
Light-chain (AL) amyloidosis;
Cardiac amyloidosis;
Heart failure;
NT-proBNP;

Abstract Chemotherapy combining cyclophosphamide, bortezomib and dexamethasone is widely used in light-chain amyloidosis. The benefit is limited in patients with cardiac amyloidosis mainly because of adverse cardiac events. Retrospective analysis of our cohort showed that 39 patients died with 42% during the first month. A new escalation-sequential regimen was set to improve the outcomes. Nine newly-diagnosed patients were prospectively treated with close monitoring of serum N-terminal pro-brain natriuretic peptide, troponin-T and free

* *Corresponding author*: Department of Cardiology, Hôpital Henri Mondor, 51 avenue du maréchal de Lattre de Tassigny, F 94000 Créteil, France.
E-mail address: thibaud.damy@aphp.fr (T. Damy).
[1] Contributed equally to this work as first author.

http://dx.doi.org/10.1016/j.ejca.2017.02.004

Free light-chains;
Dexamethasone;
Treatment;
Mortality mortality

light chains. The results show that corticoids may destabilise the heart through fluid retention. Thus, a sequential protocol may be a promising approach to treat these patients.

1. Introduction

Cardiac involvement is frequent in light-chain (AL) amyloidosis and leads to poor prognosis [1]. Risk stratification (Mayo-Clinic staging) relies on cardiac biomarkers i.e., serum cardiac troponin-T and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels at presentation. In the original description of this staging system [2], the median overall survival was 26.4, 10.5 and 3.5 months, for stage-I, II and III, respectively. Improvement of survival has been achieved by up-front chemotherapy combining cyclophosphamide, bortezomib and dexamethasone (CyBorD). This regimen allows achievement of complete haematologic remission in 65%–71% [3] of the patients and markedly prolongs their survival, with a 2-year overall survival of 94.4% at stage-III [3]. However, serious cardiac events such as sudden death, syncope, arrhythmia and heart failure often occur during the first cycle of treatment, occasionally leading to death [4].

We first analysed retrospectively 67 patients with AL cardiac amyloidosis (CA) diagnosed between 2010 and 2014 in our centre. Sixty-one percent were male. The median age was 65 (56; 71) years. Serum NT-proBNP and troponin-T were respectively 5074 (1514; 13 063) ng/L and 97 (55; 144), respectively. Twenty-six (39%) were dead, of whom 11 (42%) have died within the first month of CyBorD's initiation (10 sudden deaths). Interrogation of implanted-cardioverter-defibrillator revealed atrial/ventricular arrhythmia in the first 24 h of the chemotherapy in two cases. These results raised questions on the role of chemotherapy in some early deaths. We thus changed our protocol to an escalation-sequential treatment regimen in an attempt to improve the outcomes. The pathophysiological mechanisms in addition to the severity of the CA that might explain early cardiac events are not known, and the main hypotheses are: (1) dexamethasone might increase fluid retention and arrhythmia leading to cardiac events, as already suspected in patients treated with a 'high' dose of dexamethasone [5]. (2) plasma bortezomib concentration might increase after liver dysfunction due to right heart failure or infiltration of the liver by AL-amyloid deposits. Indeed, proteasome inhibitors, which are eliminated by the liver, are known for their cardiac toxicity [6,7]; (3) initiation of the treatment might induce acute release of dFLC with direct cardiac toxicity [8,9]. The aim of our study was to understand the underlying mechanism of this early cardiac toxicity.

2. Methods

We prospectively treated nine patients with the new protocol described below. All patients had histologically proven AL-amyloidosis. They were all informed and gave their informed written consent, and the study was approved by CPP IDF Paris VI. All patients had comprehensive clinical and biological initial evaluation including blood count, serum NT-proBNP and troponin-T, serum and urinary protein electrophoresis, serum and urinary immunofixation, serum quantification of free light-chains (FLCs), echocardiography, ^{99m}-TC-DPD scintigraphy and cardiac MRI. All the patients had elevation of the involved FLC above the reference range and an abnormal FLC-ratio. Cardiac involvement was defined according to the International Society for Amyloidosis criteria [10]. All patients were treated by CyBorD.

Our sequential protocol consisted of a weekly treatment escalation; dexamethasone was first given alone during sequence-1 (S1), cyclophosphamide and bortezomib were introduced at S2 and S3, respectively. S1 was initiated at day (d) 1, S2 at d8 and S3 at d15. The first cycle thus included: dexamethasone 20 mg, oral at d1-2 (S1), 8–9 (S2), 15–16 (S3), 22–23 (S4); cyclophosphamide 300 mg/m^2, oral at d8 (S2) and 15 (S3) and bortezomib 1.3 mg/m^2 subcutaneous at d15 (S3) and 22 (S4).

NT-proBNP, troponin-T-US and FLC were quantified at time 0, 4 h and 24 h for each sequence. NT-proBNP and troponin-T-US were measured using electrochemiluminescence kits (Roche Diagnostic, Meylan, France). Serum κ and λ FLC concentrations were determined by nephelometry using the Freelite assay (The Binding Site, Birmingham, UK) and the N-latex FLC assay (Siemens, Marburg, Germany), according to the manufacturer's instructions. The dFLC was calculated as follows: $|\kappa-\lambda|$ = difference between the involved and the uninvolved FLC. Plasma concentrations of bortezomib were measured using liquid chromatography-tandem mass-spectrometry [11] at 0, 30 min, 1 h, 2 h, 4 h and 24 h of S3.

3. Results and discussion

Baseline data of the patients who received the modified CyBorD treatment between December-2014 and July-2015 are described in Table 1. Interestingly, cardiac