Ventricular tachyarrhythmias and sudden cardiac death in light-chain amyloidosis: a clash of cardio-toxicities?

Sudden cardiac death (SCD) is not uncommon in immunoglobulin light-chain amyloidosis (AL) and has been usually attributed to pulseless electrical activity (PEA) or agonal bradycardia occurring in the late stages of the cardiomyopathy.[1,2] In addition, the historically reported survival of <12 months in patients with cardiac AL has represented a contraindication to an implantable cardioverter defibrillator (ICD).[3] Reports based on small series have further discouraged use of an ICD in this disease.[4,5] However, recently, the evolution of treatment options has improved overall survival,[6] opening new perspectives in terms of cardiac protection, and calling for further understanding of the arrhythmic profile and SCD prevention in patients with AL.

Following the repeated observation of potentially lethal ventricular tachyarrhythmias in patients with AL, we retrospectively analysed 66 consecutive patients diagnosed with AL at a tertiary referral centre (Careggi University Hospital, Florence, Italy), between January 2016 and December 2019, to assess the prevalence and clinical setting of cardiac arrest and SCD. For the purpose of this study, aborted cardiac arrest and appropriate ICD shock were considered as SCD equivalents.

The mean (SD) age of the 66 patients was 67 (10) years, 44 (67%) males. Cardiac involvement was diagnosed in 56 (84%) patients. For the main demographic, baseline features and chemotherapeutic approaches see Table S1.

At a mean (SD) of 6 (3) months from diagnosis of AL amyloidosis, eight patients (12%) had SCD. Of these, four (6%) had resuscitated cardiac arrest (of whom, one subsequently died of refractory heart failure, patient 6; Fig 1, Table I) whereas four died (Fig 1, Table I). The remaining three patients were alive at census date (September 2020), at a mean (SD) 28 (7) months from cardiac arrest (Fig 1, Table I).

All eight patients with SCD had known AL cardiac involvement, whereas cardiac involvement was present in 48 (82%) of patients not experiencing SCD. There were no statistical differences in the main clinical characteristics between patients with and without SCD, although the mean interventricular septum wall thickness was greater in patients with SCD (Table S1). The mean left ventricle ejection fraction (LVEF) between the two groups was comparable. The LVEF in patients experiencing SCD ranged from 45% (mild reduction) to 65% (normal) and in patients without SCD ranged from 30% (severely impaired) to 69%; therefore EF may prove falsely reassuring in discriminating patients at risk of SCD.

All patients with SCD underwent cyclophosphamide/bortezomib/dexamethasone (CyBorDex) as their first-line chemotherapy approach; in patients without SCD, CyBorDex was the most common type of first-line treatment accounting for 45% of chemotherapeutic approaches (Table S1).

In four of the eight patients with SCD, the presenting rhythm was a documented hyperkinetic ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation); among the remaining four patients, PEA was the presenting rhythm in one whereas in three the presenting rhythm was unknown (Table I, Fig 1). Three of the four patients with hyperkinetic ventricular arrhythmias received an ICD in secondary prevention; one patient with ventricular tachycardia did not receive an ICD because of advanced heart failure and poor life expectancy (Patient 6 Table I, Fig 1). Excluding Patient 6, all patients survived to cardiac arrest initiated antiarrhythmic therapy with β-blockers or amiodarone. One patient with an ICD had multiple appropriate shocks during follow-up (Patient 5 Fig 1). All patients with an ICD were alive at census date and classified as functional New York Heart Association (NYHA) Class II or III (Patient 5, 7, 8 Fig 1, Table I).

Of note, all patients that experienced SCD did so during chemotherapy and in only one case an appropriate shock occurred during the remission period. In seven patients, SCD occurred during CyBorDex treatment (Fig 1). One patient experienced resuscitated SCD due to ventricular tachyarrhythmia during second-line treatment with lenalidomide/dexamethasone (Patient 6, Fig 1). Furthermore, one patient with previous resuscitated SCD during CyBorDex, had an appropriate ICD shock due to ventricular tachyarrhythmia in a chemotherapy-free remission period and multiple arrhythmic events triggering ICD interventions, during daratumumab/lenalidomide/dexamethasone course for AL relapse (Patient 5 Fig 1).

We think there are two main findings in the present study:

1 Patients with AL and cardiac involvement are prone to SCD, mediated by ventricular tachyarrhythmias at least as often as atrioventricular block or PEA – contradicting a long-held belief.
2 Life-threatening ventricular tachyarrhythmias cluster almost exclusively during chemotherapy cycles, suggesting

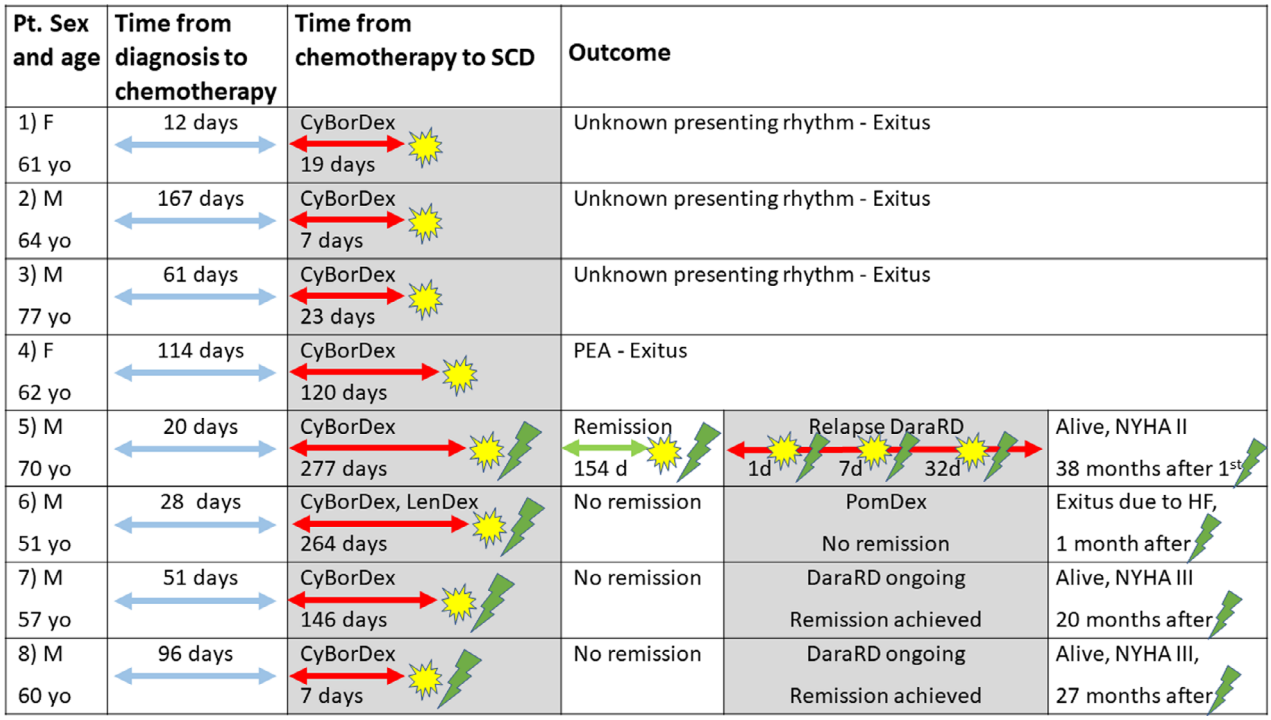

Fig 1. Time interval from chemotherapy start to sudden cardiac death/cardiac arrest (SCD) and patients outcomes. In our cohort eight patients experienced SCD. In three of the eight patients with SCD, the presenting rhythm was unknown (Patients 1, 2, 3), pulseless electrical activity (PEA) was the presenting rhythm in Patient 4 and documented ventricular tachyarrhythmia was the presenting rhythm in Patients 5, 6, 7, 8. All patients with SCD underwent cyclophosphamide/bortezomib/dexamethasone (CyBorDex) as first-line chemotherapy. All patients experienced SCD during chemotherapy. In only one case an appropriate shock occurred during the remission period (Patient 5). All patients with ventricular tachyarrhythmias had resuscitated cardiac arrest; three of them received an implantable cardioverter defibrillator (ICD), whereas one did not because of advanced heart failure (Patient 6). Patient 5 had multiple appropriate ICD shocks during disease relapse while receiving daratumumab/lenalidomide/dexamethasone (DaraRD). All patients with an ICD were alive at the census date and classified as functional New York Heart Association (NYHA) Class II or III after >20 months from resuscitated cardiac arrest (Patients 5, 7, 8). F, female; LenDex, lenalidomide/dexamethasone; M, male; PomDex, pomalidomide/dexamethasone; UNK, unknown; yo, years old; , sudden cardiac death/cardiac arrest; , external or implantable cardiac defibrillator shock following ventricular tachyarrhythmias.

that an arrhythmic propensity could be triggered by the synergistic effects of AL light chain and drug-induced cardiac toxicity.

In our present cohort four patients had ventricular tachyarrhythmias, including one with multiple events (mostly while receiving chemotherapy). Three patients received an ICD for secondary prevention (one with multiple appropriate interventions; Figure 1 and Table I). The mean (SD) survival in patients receiving an ICD after the first event was 28 (7) months and >20 months in each. Successful resuscitation after defibrillator shock therapy resulted in a meaningful survival benefit, raising the possibility that ICD implantation may be appropriate in selected cases – an issue still controversial in AL amyloidosis.[4,5]

Chemotherapy for AL amyloidosis is mainly based on regimens used for the treatment of myeloma and not specifically approved for AL cardiac involvement. Most of these drugs have established cardiotoxic potential, with increased risk of heart failure and arrhythmic events.[7]

Ventricular arrhythmogenesis in cardiac amyloidosis is not well understood. The widely accepted paradigm is that of a progressive cardiomyopathy in which myocardial infiltration leads to bradyarrhythmias and PEA in advanced stages;[1] these are generally terminal events with limited if any therapeutic potential. However, our observation suggests that, at earlier stages, the synergistic toxicity of unrestrained circulating light chains[8] and chemotherapy agents may rather trigger ventricular tachyarrhythmias.

Our hypothesis requires further, large-scale validation. Nevertheless, these observations are potentially relevant for practice, raising important clinical questions. Should we implement specific surveillance strategies? Can we identify patients at greater risk? Can we define criteria and timing for ICD implantation in primary prevention? Should we consider a critical reappraisal of chemotherapy regimens in patients with moderate-to-severe cardiac involvement due to AL amyloidosis, in order to limit cardiotoxicity? As for many other neoplastic diseases, improvements in general outcomes must

Table I. Demographic, main clinical and echocardiographic baseline features in patients experiencing sudden cardiac death.

Patient number; gender; age, years	Diagnosis	Mayo revised score	NTproBNP, pg/ml NYHA class	Tn I, ng/ml	IVS, mm	EF, %	E/e'	TAPSE, mm	sPAP, mmHg	ECG	Chemotherapy	Chemotherapy courses, *n*	Outcome
1; F; 61	MM	III	15000 NYHA III	0·11	14	65	16	19	37	SR, 87 bpm, reduced R wave progression on anterior leads, non-specific inferolateral ST segment abnormalities.	CyBorDex* *Bor 1·3 mg/m^2; Dex 40 mg qw	1	Unknown rhythm – Exitus
2; M; 64	MGUS	III	7770 NYHA III	0·04	17	50	17	18	56	SR, 64 bpm, left bundle branch block (paroxysmal atrial fibrillation).	CyBorDex* *Bor 1·3 mg/m^2; Dex 40 mg qw	1	Unknown rhythm – Exitus
3; M; 77	MGUS	IV	10891 NYHA III	0·13	18	63	23	22	42	SR, 74 bpm, low limb leads voltages.	CyBorDex* *Bor 1·0 mg/m^2; Dex 20 mg qw	1	Unknown rhythm – Exitus
4; F; 62	SM	II	1387 NYHA II	0·30	14	61	16	20	35	Sinus tachycardia, 108 bpm. Preserved atrial and ventricular conduction.	CyBorDex* *Bor 1·3 mg/m^2; Dex 40 mg qw	3	PEA – Exitus
5; M; 70	SM	IV	3025 NYHA II	1·92	20	55	22	22	28	SR, 68 bpm, right bundle branch block, left axis deviation.	CyBorDex* DaraRD *Bor 1·0 mg/m^2; Dex 20 mg qw	8 On-going	Multiple VT/VF episodes. Haematological remission achieved. Alive at census date, NYHA II
6; M; 51	SM	III	3968 NYHA II	0·12	16	45	20	16	42	SR, 68 bpm, reduced R wave progression on anterior leads, low limb leads voltages, non-specific lateral ST segment abnormalities.	CyBorDex* LenDex PomDex *Bor 1·3 mg/m^2; Dex 20 mg qw	6 1 2	VT-induced cardiac arrest. No haematological remission. Exitus due to worsening heart failure
7; M; 57	SM	III	3166 NYHA II	0·84	18	49	18	15	41	SR,68 bpm, 1st degree AV block, reduced R wave progression on anterior leads, low limb leads voltages.	CyBorDex* DaraRD *Bor 1·3 mg/m^2; Dex 40 mg qw	6 On- going	VT induced cardiac arrest. Remission achieved. Alive at census date, NYHA III

Table I. (*Continued*)

Patient number; gender; age, years	Diagnosis	Mayo revised score	NTproBNP, pg/ml NYHA class	Tn I, ng/ml	IVS, mm	EF, %	E/e'	TAPSE, mm	sPAP, mmHg	ECG	Chemotherapy	Chemotherapy courses, *n*	Outcome
8; M; 60	SM	IV	2729 NYHA III	0·17	20	62	23	16	43	SR, 78 bpm, right bundle branch block, left anterior hemi-block, anterior pseudo necrosis, low limb leads voltages.	CyBorDex* DaraRD *Bor 1·0 mg/m^2; Dex 20 mg qw	4 On-going	VT induced cardiac arrest. Remission achieved. Alive at census date, NYHA III

AV, atrioventricular; bpm, beats/min; CyBorDex, cyclophosphamide/bortezomib/dexamethasone; DaraRD, daratumumab/dexamethasone/lenalidomide; ECG, electrocardiogram; EF, ejection fraction; IVS, interventricular septum; LenDex, lenalidomide/dexamethasone; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NTproBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association class; PomDex, pomalidomide/dexamethasone; qw, quaque week (once a week); SM, smouldering myeloma; SR, sinus rhythm; PEA, pulseless electrical activity; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; Tn, troponin; VF, ventricular fibrillation; VT, ventricular tachycardia.

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enhance our attention towards cardio-oncological issues in survivors; this is a testimony to the efficacy of current treatment, but equally represents a novel challenge to cardiologists.

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Conflict of interest

None declared.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Demographic, clinical, echocardiographic characteristics at diagnosis and first-line chemotherapy at baseline.

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Are white blood cells white?

Understanding the physiology and pathology of white blood cells is routine for haematologists. But it is not often that we stopped and thought; are these white blood cells really white in colour? Most of us have almost daily encounters with these corpuscles either through a microscope or interpreting their numbers and continue to call them white blood cells, despite none of them being white. Looking at the history of its nomenclature is fascinating in this respect.

In the century following Antonie van Leeuwenhoek's description of the red blood corpuscles, Joseph Lieutaud (personal physician of King Louis XVI), first reported white cells as 'globuli albicantes' (white globules).[1,2] Another