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Treatment of light chain deposition disease with bortezomib and dexamethasone

Light chain deposition disease (LCDD) is a rare plasma cell dyscrasia characterized by deposition of immunoglobulin fragments. The kidneys are almost always affected while heart, liver and other tissues are occasionally involved. About 50% of patients with LCDD have concurrent myeloma, however most present with nephrotic range proteinuria and rapidly deteriorating renal function.[1] Renal biopsy shows nodular glomerulosclerosis, resembling diabetic kidney changes, and linear deposits of monoclonal light chains along tubular basement membrane by immunofluorescence. The depositions are granular or amorphous and non-fibrilar, Congo-red negative.[2] The outcome of patients with LCDD is variable. Median time to end-stage renal disease (ESRD) is 2.7 years with 5-year ESRD-free survival of 37%.[2] There is no standard treatment for patients with LCDD. Chemotherapy with alkylating agents and steroids has shown modest results.[3,4] High-dose melphalan (HDM) with autologous stem cell transplantation (ASCT) has been used in some patients and has led to improvement of renal function.[5,6] Bortezomib, a reversible proteasome inhibitor, has shown significant activity in myeloma patients and is safely administered to patients with renal failure, even those under dialysis.[7] Preliminary experience indicates that bortezomib is associated with hematologic and organ responses in patients with light chain amyloidosis.[8] Recent data indicate that this agent may have a protective role of renal parenchyma due to inhibition of NFκB activity.[9] Based on the above data we administered the combination of bortezomib and dexamethasone to 4 consecutive patients with LCDD with typical findings of renal biopsy, serum and urine electrophoresis, and immunofixation and bone marrow biopsy (Table 1). None of the patients had symptomatic myeloma defined by osteolytic bone disease, hypercalcemia, anemia or renal impairment due to myeloma cast nephropathy. Two patients were previously untreated; one was relapsing from prior response to cyclophosphamide with prednisone and one was refractory to vincristine, doxorubicin and dexamethasone (VAD). All patients presented with impaired renal function, non-selective proteinuria and poorly controlled hypertension, defined as blood pressure (BP) > 140/90 mmHg, although they were receiving three or more antihypertensive drugs (Table 1). One patient also had echocardiographic evidence of heart involvement. Serum free light chains (FLCs-FREELITE assay) were elevated in all patients, with abnormal kappa to λ ratio, and were measured at the beginning of each cycle of treatment. Three patients had no measurable monoclonal

Table 1. Patients' characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4
Gender/Age (years)	Female/56	Male/46	Male/52	Male/67
Prior therapy	N/A	VAD (refractory)	N/A	Cyclophosphamide/prednisone (relapse off treatment)
Bone marrow plasma cells	20%	10%	11%	3%
Light chain type	κ	κ	κ	λ
Serum immunofixation	κ	0	IgG-κ	0
Urine immunofixation	κ	κ	κ	λ
Pre/post BD involved free light chain (mg/L)	2670/76.1	523/13.6	297/24.5	232/99.4
Pre/post BD (κ/λ ratio)	252/6.5	54.4/ 0.95	11/0.9	0.2/0.47
Pre/post BD creatinine (mg/dL)	3.6/1.7	2.1/1.8	3.5/2.4	2.4/1.7
Pre/post BD 24h urine protein (mg)	2860/375	6500/416	4920 / < 200	1620 / 680
Pre/post BD serum albumin (gr/dL)	3.2/3.9	3.3/4.2	3.7/4.4	4/4
Pre/post BD antihypertensive treatment	3 drugs/1 drug	3 drug/2 drugs	5 drugs/2 drugs	5 drugs/3 drugs
Response to BD	PR	CR	CR	PR
Time to response (>50% reduction of affected light chain by FREELITE)	21 days (1 cycle of BD)	21 days (1 cycle of BD)	21 days (1 cycle of BD)	84 days (4 cycles)
Time to hematologic CR (Normal free light chains and ratio)	N/A	63 days (3 cycles of BD)	84 days (4 cycles of BD)	N/A
Time to 50% reduction 24h urine protein	42 days (2 cycles of BD)	21 days (1 cycle of BD)	42 days (2 cycles of BD)	63 days (3 cycles of BD)
CD34 collection (*10^6/Kg)	15	63	8	N/A
Time to neutrophil engraftment	Day 8	Day 10	Day 11	N/A
Months without progression	16+	15+	12+	At 2 months relapse of proteinuria without hematologic relapse

protein by electrophoresis and FLCs were used to assess hematologic response. All patients received the combination of bortezomib (B) 1.3 mg/m^2 on days 1,4,8,11 and dexamethasone(D) 40 mg on days 1-4 every 21 days for up to 6 cycles. Patients provided informed consent for the compassionate use of bortezomib. The hospital's review board granted permission to review and report data from the files of the patients. Hematologic responses to BD were rapid and 2 patients achieved a CR, with a normal FLC ratio while the other 2 had >50% decrease of the involved light chain. Table 1 shows details of the hematologic response, reduction of proteinuria and improvement of renal function. After BD all patients achieved adequate control of hypertension, defined as BP <120/80 mmHg, with less than half of the drugs that they were using before treatment. The toxicity of the combination was manageable. Because of peripheral neuropathy, the dose of bortezomib was reduced to 1 mg/m^2 and to 0.7 mg/m^2 in 2 patients respectively and one patient received 5 cycles of BD. Other side effects included mild and transient orthostatic hypotension, transient elevation of liver enzymes and constipation. Three patients subsequently proceeded to HDM with ASCT: 2 patients while in CR after BD and one in PR. Two were mobilized with cyclophosphamide and G-CSF and one with G-CSF alone. The dose of melphalan was 140 mg/m^2 based on creatinine clearance prior to HDM. There were no complications related to stem cell harvest and engraftment (Table 1). After HDM, all 3 patients are in hematologic CR with only trace proteinuria.

The patient with heart involvement showed improvement of his diastolic dysfunction and minor improvement in the thickness of intreventricular septum by 1mm. After a follow-up of 10-18 months, all patients are alive but in the patient who was not candidate for HDM, proteinuria recurred two months after he stopped VD, although criteria for hematologic relapse were not yet fulfilled.

This is the first report of the use of bortezomib in the treatment of LCDD. Despite the small number of our patients we provide evidence that BD is active in this rare disease. Rapid reduction of toxic light chains is mandatory in LCDD since continuing deposition may rapidly deteriorate organ function.[3] With BD, hematologic responses were rapid and were accompanied by rapid and significant reduction of proteinuria and by improvement of renal function. As is also the case in patients with amyloidosis, the measurement of serum free light chains was useful in the follow-up of our patients with LCDD and the reduction of involved light chains was associated with a significant improvement in proteinuria.

The rapid reduction of toxic light chains after treatment with BD resulted in the improvement of renal function, however pre-clinical data indicate that there may be additional mechanisms for the beneficial effect of BD in LCDD. In LCDD, toxic monoclonal light chains interact with receptors in mesangial cells initiating a cascade of activation of pathways that include the NFκB pathway. NFκB activation results in stimulation of cytokine production causing attraction of inflammatory cells. PDGF-β and TGF-β are also induced by light chain–mesangial cell interaction in LCDD. This results in cell proliferation and activation of genes responsible for collagen and tenascin production, resulting in dramatic changes in mesangial matrix, leading to the pathological picture of glomerulosclerosis.[10] Bortezomib inhibits the NFkB pathway,[11] decreases TGF-β1 levels and may down-regulate collagen and TIMP-1 production.[12,13] Thus, bortezomib may interrupt the cascade that leads to rapid renal deterioration through these pathways by inhibiting progression of glomerulosclerosis, and may improve glomerular function thus reducing proteinuria. Nevertheless, demonstration of a bortezomib effect on the inflammation in renal parenchyma would have required repeated renal biopsies which were not performed.

HDM with ASCT has been used in small series of patients with LCDD and has resulted in durable responses and improvement of renal function.[5,6] However in patients with impaired renal function this procedure is associated with increased mortality and significant toxicity. In all our patients who underwent HDM, toxicity was acceptable. We conclude that BD appears to be an active combination that results in rapid hematologic responses, rapid decrease of proteinuria and improvement of renal function in patients with LCDD. If others confirm our data, BD may become the preferred initial treatment for patients with LCDD.

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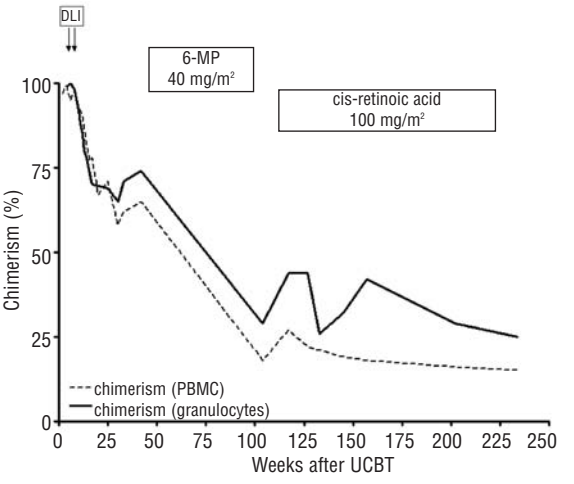

Figure 1. DLI: donor lymphocyte infusion (week 10 and 12); 6-MP: 6-mercapto-purine; PBMC: peripheral blood mononuclear cells; UCBT: umbilical cord blood transplantation; % chimerism reflects the percentage of donor bone marrow in the patient.

HLA-identical umbilical cord blood transplantation from a sibling donor in juvenile myelomonocytic leukemia

As recently described by Flotho *et al*. juvenile myelomonocytic leukemia (JMML) is a rare type of childhood leukemia not only characterized by young age, hepatosplenomegaly, thrombocytopenia and monocytosis, but also by molecular aberrations in the RAS-RAF-MEK-ERK signaling pathway and GM-CSF-hypersensitivity.[1] Although progress has been made in unraveling the molecular background of JMML, the only curative treatment option for these children is stem cell transplantation (SCT).[2,3] Previous studies have shown that in JMML the graft versus leukemia (GvL) effect of the SCT plays an important role in the prevention of relapse.[2,4] Hence, donor and stem cell source selection could play an important role in the outcome of JMML patients. SCT using unrelated, immunological naive, umbilical cord blood (UCB) has shown to be effective for pediatric JMML.[3] UCBT has increased the available pool of hematopoietic stem cell transplantation donors, especially for young children.[5] This is important for patients with rare HLA-haplotypes and with diseases that may rapidly progress like JMML. However, it is conceivable that the relatively immunological naivety of cord blood stem cells from a newborn HLA identical sibling donor may be a negative factor for outcome.[4,6]

In this report we describe 5 JMML patients registered in the database of the European Working Group on Childhood MDS (EWOG-MDS), who have received umbilical cord stem cells from an HLA-identical sibling (Table 1). So far only MacMillan *et al*. has described a JMML patient who received HLA-identical sibling umbilical cord cells.[7] More information is available on unrelated UCBT in JMML.[3,7,8] Recently, from the combined EWOG-MDS/EBMT registry, Locatelli *et al*. described 100 JMML patients of whom 7 received an unrelated UCBT. These 7 patients showed a delayed hematologic recovery, but the outcome was comparable to the children treated with other stem cell sources.[3] Rocha *et al*. reported that children receiving a related UCBT for malignancies, bone marrow failure syndromes, hemoglobinopathies, inborn errors of metabolism or immunodeficiencies, had a slower hematopoietic recovery and a lower risk of acute and chronic GVHD than children receiving a related bone marrow transplantation.[9] Gluckman *et al*. have shown that the amount of acute GVHD in related UCBT is lower (18%) than in unrelated UCBT (32%).[10] These studies underscore the relative immune naivety of the UCB cells and the feasibility of the use of UCBs especially for childhood transplantation settings. However, especially in JMML, where the GvL-effect is an important contributor to the success of the transplantation procedure, it could be questioned whether these relatively naive umbilical stem cells from sibling donors should be used in all patients, especially when alternative donors would be available.

In all cases full donor-chimerism was found after transplantation. In the cases that relapsed, a mixed chimerism was found prior to clinical progression. In addition, in Patient 1 increasing mixed donor-chimerism developed from day 42 onwards without clinical signs of relapse (Figure 1). Mixed donor-chimerism after SCT in JMML has been shown to be an important predictor for relapse, therefore discontinuation of immunosuppressive therapy (IST) is the first step to prevent relapse if this occurs early after transplantation.[11] To avoid relapse, a second stem cell transplantation was considered, but the parents were very reluctant to proceed, because of the absence of any clinical signs of JMML and the excellent clinical condition of the child. Therefore, 6-mercaptopurine (6-MP) (average dose 40 mg/m^2) was started on day 145 after SCT. When, after initial improvement, donor-chimerism increased, 6-MP was replaced by 13-cis-retinoic acid (100 mg/m^2/day every other week) for 2.5 years until the age of five years. Thereafter, the child remained well with a current follow-up of five years after SCT. At present the percentage of donor cells is 15%, without any clinical sign of JMML. At the moment no series are available on the use of 6-MP and 13-cis-retinoic acid in a relapse setting after SCT for JMML. Although Locatelli *et al*. showed that second SCT was successful in 7/15 cases with a relapse after SCT, the issue whether to proceed to a second SCT in all cases of