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ORIGINAL ARTICLE

Bortezomib-based chemotherapy can improve renal and tubular functions in patients with light chain-associated Fanconi syndrome

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Abstract

Light chain-associated Fanconi syndrome (LCFS) is a disorder of renal proximal tubule due to immunoglobulin light chains. Cases of LCFS are rare and mostly sporadically reported, and treatment of this entity is still controversial. This single-center retrospective study included 22 patients diagnosed with LCFS in Peking Union Medical College Hospital. Monoclonal gammopathy of undetermined significance was diagnosed in 13 patients, and overt multiple myeloma in six patients, with two smoldering myeloma and one Waldenstrom macroglobulinemia. Light chain was mostly kappa type (90.9%). Baseline median estimated glomerular filtration rate was 66 (13–126) ml/min/1.73 m^2, with one patient presented as end-stage renal disease. After a median follow-up of 37 months, three patients died. Twelve patients were treated with chemotherapy, including 7 with bortezomib-based regimens. Renal function was significantly improved in the group of patients who received chemotherapy ($p = 0.026$). Compared with other chemotherapy regimens, patients with bortezomib-based treatment had a better hematological response ($p = 0.027$) as well as a better proximal tubule outcome ($p = 0.015$). Chemotherapy likely outweighs supportive treatment in patients with LCFS. Bortezomib-based regimen seems to be a safe first-line therapy for management of those patients.

Keywords Light chain-associated Fanconi syndrome · Bortezomib · Plasma cell · Renal function · Tubular function

Introduction

Light chain-associated Fanconi syndrome (LCFS) is a rare complication of plasma cell dyscrasias. Most cases are associated with monoclonal gammopathy of undetermined significance (MGUS); others include multiple myeloma (MM), overt lymphoid malignancy, and Waldenstrom macroglobulinemia (WM). Apart from the presence of monoclonal proteins, typical LCFS is characterized by the impairment of renal proximal tubules, resulting in type II proximal renal tubular acidosis, glycosuria with normal glycemia, aminoaciduria, and uricosuria with hypouricemia.

In the past decades, treatments of LCFS mainly focused on the supplementation of electrolytes to alleviate the symptoms of Fanconi syndrome [1]. Meanwhile, chemotherapy was usually deferred in patients with MGUS, due to the slow disease progression, as well as the adverse events after chemotherapy [2]. During recent years, with new drugs available for anti-myeloma therapy, more isolated case reports and small case series seem to favor aggressive therapies for LCFS [3–5]. Vignon et al. [6] recently published a series of 49 patients, most of whom received chemotherapy and obtained hematological response, together with stable renal function; notably, 13 patients who received chemotherapy had improved tubular function.

We retrospectively reviewed a series of 22 patients with LCFS in Peking Union Medical College Hospital, in an attempt to delineate the clinical characteristics and outcomes of LCFS in China and to compare different treatment options in the modern treatment era.

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Study design

Patients

All the patients were diagnosed with LCFS in Peking Union Medical College Hospital from January 2000 to April 2018. A written informed consent was obtained from each patient. This study was approved by the Ethics Committee of the hospital.

Demographic and clinical information, including sex, age, clinical symptoms, physical examination, laboratory results, radiological findings, bone marrow examination, renal biopsies, and treatment strategies, were documented. Serum creatinine (Cr) was measured using an enzymatic method. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation [7]. Proximal tubular function was examined through the following tests: serum phosphate and uric acid; urine glucose and amino acid; 24-h urine excretion of phosphate, potassium, sodium, and calcium; urine β-2-microglobulin (β2MG); urine α-1-microglobulin (α1MG); urine transferrin; urinary N-acetyl-beta-D-glucosaminidase activity/creatinine ratio (NAG/Cr); renal tubular reabsorption of phosphate (TmP/GFR); and albumin to creatinine ratio (ACR).

All patients exhibited both monoclonal gammopathy and Fanconi syndrome. Diagnoses of MGUS and MM were made according to the International Myeloma Working Group criteria in 2014 [8]. WM was diagnosed based on the World Health Organization criteria in 2016 [9]. Patients with full-blown Fanconi syndrome fulfilled all of the five criteria, including proximal renal tubular acidosis, glycosuria with normal glycemia, hypouricemia, aminoaciduria, and hyperphosphaturia; while incomplete Fanconi syndrome met at least three of the above. Exclusion criteria were the presence of other causes of Fanconi syndrome, and other renal and tubular damage induced by monoclonal gammopathy, such as light chain amyloidosis.

Hematological responses were assessed according to the International Society of Amyloidosis consensus response criteria, based on the difference between involved and uninvolved free light chains (dFLC) [10]. Chemotherapy-related toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (National Cancer Institute, Bethesda, MD) [11]. Renal response was defined by an increase in eGFR > 30% and last more than 3 months [6]. Tubular response was defined by > 50% decreases or increases, or back to the normal range of at least three of the above proximal tubular functional tests, with stable eGFR, and last for 3 months.

Statistical analysis

Categorical variables are presented as numbers (percentage), and quantitative data are presented as median value (minimum to maximum) or mean value (± standard deviation). Student's *t* test or Mann-Whitney *U* test was used for continues variables, and Fisher's exact test was used for comparing categorical variables between two groups. For all analyses, the significance end point was set to $p = 0.05$. All analysis was computed using SPSS statistics V.22.0 (SPSS Inc., Chicago, IL).

Results

Clinical characteristics

From January 2000 to April 2018, 25 patients were identified. Two patients were excluded due to the concurrent AL amyloidosis. Another one patient was excluded because the possibility of drug-related Fanconi syndrome could not be ruled out. Finally, 22 patients were included in this study, of whom 8 were men and 14 were women (Table 1). The median age was 49 years (range, 30–76 years). Most patients (72.7%) had chief complaints of bone pain, and other symptoms included hypodynamia (40.9%), myasthenia (22.7%), proteinuria (36.4%), and polyuria (13.6%). The median interval from onset of symptoms to diagnosis was 35 months (range, 4–85 months).

For the types of monoclonal protein in LCFS, kappa was found in 20 (90.9%) patients and lambda in 2 (9.1%). Heavy chain isotype was IgG ($n = 6$), IgA ($n = 4$), and IgM ($n = 1$). The rest of the 11 (50.0%) patients had light chain kappa only. For underlying malignancies, 6 (27.3%) patients were

Table 1 Clinical characteristics of 22 patients at diagnosis

Demographic characteristics	
Patients	*N* = 22
Male/female	8/14
Age, median (range)	49 (30–76)
Hematological diagnosis	
Light chain isotype	
Kappa, *N* (%)	20 (90.9%)
Lambda, *N* (%)	2 (9.1%)
Heavy chain isotype	
IgG, *N* (%)	6 (27.3%)
IgA, *N* (%)	4 (18.2%)
IgM, *N* (%)	1 (4.5%)
Light chain only	11 (50.5%)
Underlying malignancy	
MM, *N* (%)	6 (27.3%)
sMM, *N* (%)	2 (9.1%)
MGUS, *N* (%)	13 (59.1%)
WM, *N* (%)	1 (4.5%)

MGUS, monoclonal gammopathy of undetermined significance; *MM*, multiple myeloma; *sMM*, smoldering multiple myeloma; *WM*, Waldenstrom macroglobulinemia

diagnosed with overt MM; 13 (59.1%) were MGUS; two (9.1%) was smoldering MM; and one WM.

At diagnosis, the median serum creatinine level was 93 μmol/L (range, 38–348), and median eGFR was 66 ml/min/1.73 m^2 (range, 13–126). Seven (31.8%) patients had eGFR less than 60 ml/min/1.73 m^2. Initially, one patient was already diagnosed with end-stage renal disease (ESRD) and required hemodialysis. Median urine protein level was 3.1 g/day (range, 0.1–10.3 g/day). As for proximal tubular function, aminoaciduria was found in 19 out of 21 (90.5%) patients; orthoglycemic glycosuria, hypouricemia, and tubular acidosis was in 18 (81.8%) patients, and hypophosphatemia was in 19 (86.4%) patients. The results of other proximal tubular tests are listed in Table 2. Overall, 17 (77.3%) patients had full-blown Fanconi syndrome.

As for bone metabolism, osteoporosis was diagnosed in 13 out of 17 patients (76.5%). Stress fractures occurred in 11 (50.0%) patients, with nine cases in rib, four in vertebra, three in femoral neck, two in hip bone, and one in radius. Serum alkaline phosphate and β-isomerized C-terminal telopeptide levels were elevated in 81.8% and 92.3% cases, respectively. Meanwhile parathyroid hormone, $1,25(OH)_2D_3$ and total 25(OH)D levels were elevated in 18.8% (3/16), 25.0% (3/12), and 0 (0/12) cases, respectively. Serum calcium was decreased in 31.8% cases.

Renal biopsies were performed in 10 (45.5%) patients. By light microscopy (LM), droplets ($n = 1$) and vacuoles ($n = 3$) were observed in the cytoplasm of tubule cells. No crystalline inclusions were observed under LM. Seven showed various non-specific lesions of the tubule, including flattening of the epithelium cells of tubule, enlarged tubule lumen, segmental edema, and loss of brush border. Tubular focal atrophy and interstitial fibrosis with infiltration of monocytes and lymphocytes were mild to moderate in nine patients. Mild thickening of tubule basement membrane was found in four patients.

Table 2 Tubular function of 22 patients at diagnosis

Tubular function	
Aminoaciduria	19/21 (90.5%)
Orthoglycemic glycosuria	18/22 (81.8%)
Hypophosphatemia	19/22 (86.4%)
Hypouricemia	18/22 (81.8%)
Tubular acidosis	18/22 (81.8%)
Elevated urine β2MG (mg/L)	16/17 (94.1%)
Elevated urine α1MG (mg/L)	13/14 (92.9%)
Elevated urine NAG/Cr (U/mmol)	9/9 (100%)
Elevated urine TRF (mg/L)	6/7 (85.7%)
Elevated ACR (mg/mmol Cr)	7/7 (100%)
Lowered TmP/GFR (mmol/L)	11/11 (100%)
Elevated urine potassium (mmol/24 h)	4/4 (100%)
Elevated urine sodium (mmol/24 h)	6/9 (66.7%)
Elevated urine calcium (mmol/24 h)	11/16 (68.8%)

β2MG, β-2-microglobulin; *α1MG*, α-1-microglobulin; *NAG/Cr*, N-acetyl-beta-D-glucosaminidase activity/creatinine ratio; *TRF*, transferrin; *ACR*, albumin to creatinine ratio; *TmP/GFR*, renal tubular reabsorption of phosphate

Treatment and outcome

After diagnosis of LCFS, ten patients did not receive any chemotherapy nor autologous stem cell transplantation (ASCT), including one patient with MM who refused chemotherapy, one patient with smoldering MM, and eight MGUS. These ten patients only had supplementary drugs for electrolytes after diagnosis. The rest of the 12 patients received chemotherapy in addition to supplementary drugs, including five patients with MGUS. Immunomodulatory drugs were used in nine patients, which included thalidomide with dexamethasone ($n = 7$), lenalidomide with dexamethasone ($n = 1$), and thalidomide, melphalan, and dexamethasone ($n = 1$). Seven patients had bortezomib-based chemotherapy, including two with subsequent ASCT, and four with previous ineffective immunomodulatory drugs.

Median follow-up time was 37 months (range, 1–96 months). Three patients died, including one patient died of MM progression (the one diagnosed with MM while refused chemotherapy), one died of cerebral hemorrhage, and one died of an unknown reason. For chemotherapy regimens, bortezomib-based therapy and ASCT seemed to have the best hematological responses: of the six patients treated with bortezomib available for assessment of hematological responses, two reached complete response (CR), two very good partial response (VGPR), and two partial response (PR). As for ASCT, one patient had CR, and one PR, respectively. For immunomodulatory drugs, seven patients were available for assessment, including three PR, three stable disease (SD), and one progressive disease (PD) (Table 3). Toxicities of chemotherapies were common but mild. Overall, four patients treated with thalidomide developed constipation, including three grade 1 and one grade 2. Two patients with thalidomide had grade 1 fatigue. Grade 1 peripheral neuropathy occurred in two patients with bortezomib. None of the patients ceased nor changed regimens due to the adverse events.

According to our definition, renal response was achieved in 40.0% (2/5) patients using bortezomib, 25.0% (2/4) patients with immunomodulatory drugs, and 50.0% (1/2) patients with ASCT. None of the patients later developed ESRD. When we compared the two groups of patients with and without chemotherapy, statistical analysis showed no difference with respect to sex category, age at diagnosis, and the hematological, renal, and tubular laboratory results at baseline, while renal function was significantly improved in the group of patients who received chemotherapy ($\triangle$eGFR%, $-8.9 \pm 5.5\%$ vs. $12.1 \pm 23.7\%$, $p = 0.026$) (Fig. 1). Interestingly, patients with

Table 3 Hematological and renal responses of patients who received chemotherapy

	Bortezomib ($n = 7$)	Immunomodulatory drugs ($n = 9$)	ASCT ($n = 2$)
Hematological response			
CR	2/6	–	1/2
VGPR	2/6	–	–
PR	2/6	3/7	1/2
SD	–	3/7	–
PD	–	1/7	–
Renal response	2/5	1/4	1/2
Tubular response	5/6	3/7	2/2

CR, complete response; *VGPR*, very good partial response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease

bortezomib-based regimens (including two with ASCT) had a high response rate of proximal tubular function (5/6) (Fig. 2), while patients with immunomodulatory drugs (3/7) had a relative low response rate. When compared with other chemotherapy regimens, patients with bortezomib-based treatment had a better hematological response ($p = 0.027$) as well as a better tubular outcome ($p = 0.015$).

Discussion

LCFS is a rare plasma cell disorder with less than 150 cases reported so far [2, 4, 6, 12–14]. The best treatment strategies for LCFS remained unknown due to lack of clinical trials and prospective studies. We report the largest single-center cohort of LCFS in China with detailed clinical and pathological studies, and hematological, renal, and tubular outcomes in the modern era. Nearly two thirds of LCFS cases in China were female, which was quite opposite to the previous reports in western countries [2, 6]. Although in most cases immunoglobulin light chains are kappa type, there are still a minority of patients presented as lambda type, as it occurs in our cohort as well as in previous case reports [6, 14]. The hematological disorders of the most cases with LCFS are MGUS, with overt MM being the next. In addition, WM, an IgM monoclonal gammopathy, is rare but can occur in LCFS, as presented in our cohort and another series [15] and confirmed by in vivo studies [16].

Diagnosis of LCFS is sometimes challengeable and can take a certain period, especially with misleading clinical presentations of bone pain and renal dysfunction. In this study, most patients had a chief complaint of bone pain. In such situation, laboratory tests related to bone metabolism were performed, and to find osteoporosis, hypophosphatemia, elevated serum alkaline phosphate, and elevated PTH. Therefore, we suggest when typical laboratory results of FS are presented in an adult without other causes, tests of monoclonal proteins can be done to screen for LCFS.

Besides bone pain, stress fractures occur in nearly half of our patients with LCFS, which affects life quality a lot. Therefore, supplementary treatment of phosphate, calcium, and correction of acidosis can quickly relieve bone pain and improve life quality, especially for the patients without heavy tumor burden. However, at the same time, we cannot neglect that renal and tubular function will not improve simply through supplementary treatment, as long as monoclonal gammopathy exists.

LCFS is an indolent disease, with only a small number of patients developed ESRD, and more patients presented with chronic kidney disease for years. Some previous studies are against chemotherapy, mainly because of the ineffectiveness to improve proximal tubular and renal function, meanwhile bringing adverse effects [1, 12]. Additionally, as the case

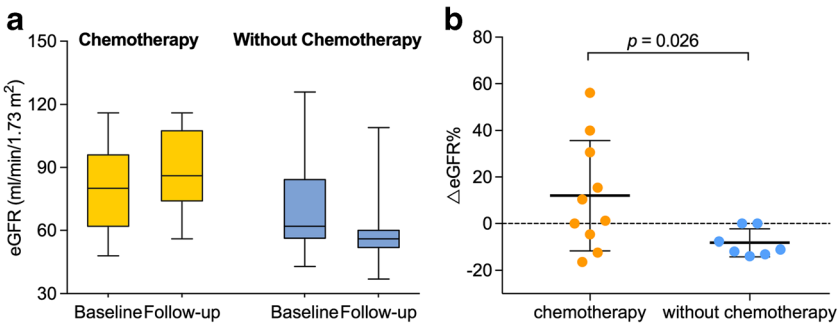

Fig. 1 Treatment response of renal and tubular function in patients with LCFS. **a** Change of eGFR in response to treatment with and without chemotherapy. **b** Comparison of △eGFR% between the patients treated with and without chemotherapy

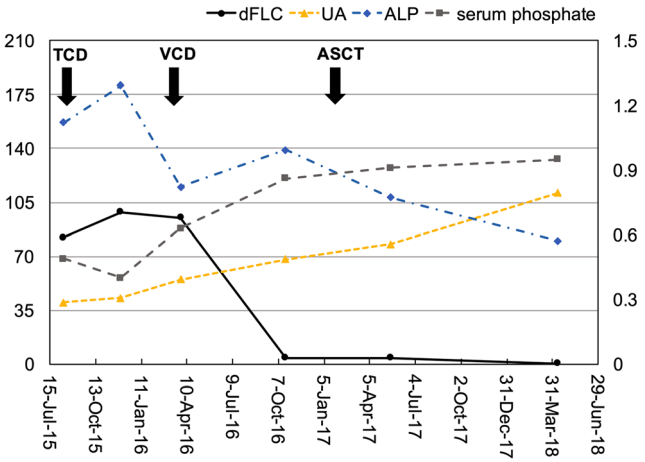

Fig. 2 Evolution of tubular function according to dFLC in one patient. TCD, thalidomide, cyclophosphamide, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; ASCT, autologous stem cell transplantation; UA, urinary acid; ALP, alkaline phosphatase

presented by Mori et al. [13], LCFS usually exhibited a benign and slowly progressive course, and even with only supportive treatment, renal functional may stay stable for years. On the other side, as new drugs come to forth and become available to more patients, complete renal and tubular response has been reported in patients using bortezomib, high dose melphalan, and ASCT [4, 6]. In this study, we found LCFS patients who received chemotherapy had significantly better renal outcomes compared with those only received supplementary treatment. Forty percent of patients experienced renal improvement during chemotherapy, in comparison with none improved during supplementary treatment. Meanwhile in our series, patients treated with chemotherapies had proximal tubular function remarkably improved, especially the ones treated with bortezomib-based regimens, which leads to a recommendation of bortezomib-based regimen as first-line therapy in LCFS. Moreover, a study from Vignon et al. [6] found bortezomib lead to early and serve neurotoxicity in 3/11 patients. However, in our series, none of the severe side effects was observed in bortezomib-based regimen ($n = 7$). One of the possible reasons was that bortezomib was used at a dosage of 1.3 g/m^2 on days 1, 8, 15, and 22, instead of on days 1, 4, 8, and 11 in our study.

This study has several limitations. First, it is a retrospective study with a small number of cases included. Due to the financial concern and previous uncertainty of the effectiveness of chemotherapy in LCFS, nearly half of the patients only received supplementary treatment. Second, the underlying plasma cell dyscrasia may influence the choice of therapy; thus, it could be uncertain if better renal and tubular outcomes in patients with chemotherapy relate directly to the therapy or to the underlying diseases. More evidence is needed in the future to draw a firm conclusion.

In conclusion, our study found that chemotherapy likely outweighs supportive treatment in patients with LCFS. Bortezomib-based regimen seems to be a safe first-line therapy for management of those patients. However, there is still lack of data regarding the role of ASCT in LCFS. Prospective larger studies are needed to support our results and to determine the optimal treatment for LCFS.

Authors' contributions XW designed and performed the study and took the lead in writing the manuscript. LZ, JF, YM, XC, and DZ performed the study and revised the manuscript. JL conceived the original idea, designed and performed the study, and revised the manuscript.

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Compliance with ethical standards A written informed consent was obtained from each patient. This study was approved by the Ethics Committee of the hospital.

Conflict of interest The authors declare that they have no conflict of interest.

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