Research Paper

Clinical Efficacy of Lenalidomide Combined with Bortezomib in the Treatment of Multiple Myeloma Nephropathy

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Multiple myeloma combined with nephropathy is one main cause of death in patients; we started this study to discuss the clinical efficacy and incidence of adverse effects of lenalidomide combined with bortezomib in multiple myeloma nephropathy treatment. We randomly selected eighty multiple myeloma nephropathy patients in Hematology Department of the First People's Hospital of Taizhou City from March 2020 to September 2021, then divided them into observation group (40 cases received lenalidomide combined with bortezomib treatment) and control group (40 cases received bortezomib treatment). Compared both groups on serum immunoglobulin, light chain protein concentration, blood creatinine, blood uric acid and nephropathy before and after therapy and also compared the clinical efficiency and the occurrence of adverse reactions. Observation group possessed remarkably higher clinical efficiency (92.5 %) than control group (82.5 %) ($p<0.05$); it possessed obviously smaller decrease of immunoglobulin, light chain protein concentration level, serum creatinine, blood calcium and blood uric acid than control group ($p<0.05$); its adverse reactions occurrence (17.5 %) had no obvious dereference from control group (20.0 %) ($p<0.05$); its adverse reactions rate (17.5 %) had no obvious dereference from control group (20.0 %) ($p<0.05$). Lenalidomide combined with bortezomib has better clinical efficacy in treating multiple myeloma nephropathy, can effectively improve renal function, has greater clinical efficacy and does not increase adverse reactions rate, so it is worth popularizing in clinic.

Key words: Lenalidomide, bortezomib, multiple myeloma nephropathy, clinical efficacy

Acute Kidney Injury (AKI) is a frequent complication of symptomatic Multiple Myeloma (MM), factors associated with kidney damage in MM include; cast nephropathy, hypercalcemia, hyperuricemia, renal amyloidosis, hyper viscosity, tumor cellular infiltration, cryoglobulinemia and so on[1]. It is caused by monoclonal Free Light Chains (FLC) with Tamm-Horsfall Protein (THP) precipitated in distal tubules, results in renal tubular obstruction, interstitial inflammation and ultimately irreversible Interstitial Fibrosis and Tubular Atrophy (IFTA)[2]. Histologically, the features of Light Chain Cast Nephropathy (LCCN) are intratubular protein casts under light microscopy and LCCN in MM often results in severe and irreversible AKI[3]. Severe renal damage will affect the sensitivity and tolerance of chemotherapy and even affect the survival of patients[4]. The benefit of renal biopsy in MM patients with renal insufficiency is controversial. The International Myeloma Working Group (IMWG) recommends that biopsy should not be considered when LCCN is highly suspected (high serum FLC levels and predominant LC proteinuria patients)[5]. Introduction of new drug improves MM's survival, even in severe renal insufficiency patients[6]. However, poor renal function may reduce drug tolerance and restrict treatment options and bortezomib is approved for relapsed MM treatment, studies have shown that bortezomib can induce complete tumor response and significantly prolong survival[7]. Lenalidomide is used as a first-line treatment for MM and is also approved for mantle cell lymphoma, it is effective for Myelodysplastic Syndrome (MDS) associated with isolated deletion of chromosome 5q MDS (del5q-MDS)[8]. Therefore, discuss the clinical efficacy of lenalidomide combined with bortezomib in MM nephropathy therapy and its effect on renal function and immune globulin in patients, in order to find safe and effective methods to improve the clinical efficacy and prognosis of MM nephropathy patients, the report is as follows. The study

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belongs to a double-blind randomized clinical trial, with a collection of 80 MM nephropathy patients in the Hematology Department of our hospital, informed the patients that after drug treatment, there will be still poor improvement of renal function and the patients signed an informed consent form to be included in the study. Then divided them into observation group (40 cases received lenalidomide combined with bortezomib therapy) and control group (40 cases received bortezomib therapy). Patients met the standard for MM nephropathy in the "Guidelines for the diagnosis and treatment of MM in China (the 4th edition)"[9]; understand research needs, cooperate with doctors and sign informed consent. Have a medical condition (such as heart disease, high blood pressure history, etc.) or a history of major surgery; allergic to bortezomib or lenalidomide; patients with mental disorders; pregnant or postpartum patients were excluded from the study. The general data, onset time and clinical symptoms of both groups were comparable ($p>0.05$). Both groups were given conventional symptomatic and supportive treatment such as kidney protection, liver protection and fluid replacement, control group received bortezomib (Xi'an Janssen Pharmaceutical Co., Ltd., national medicine permission number: J20120055) treatment, the therapeutic dose is 1 mg/m^2, hypodermic injection on the 1st, 4th, 8th and 11th d; after receiving the same treatment, observation group received another lenalidomide (Qilu Pharmaceutical Co., Ltd., national medicine permission number: H20193115), 25 mg/time, once a day. Every 21 d is a course of treatment. After 2 courses of treatment, evaluated the related clinical effective rates of both groups of patients. Collected 5 ml of fasting cubital vein blood from both groups in the early morning of 2 d after admission and after 2 courses of treatment and divided them into two centrifuge tubes, each tube 3 ml. Left one tube standing under room temperature condition for 30 min; then centrifuged for 10 min at 3500 r/min centrifuge (4°), performed supernatant extraction, used enzymatic method and uricase method to detect renal function in peripheral blood serum, including serum creatinine and serum uric acid levels. Sent to Huada Company to detect the concentration of Immunoglobulin (Ig) and light chain protein in serum, checked the occurrence of adverse reactions of patients. The clinical efficacy was determined according to the "Guidelines for the diagnosis and treatment of MM in China (the 4th ed)"[9], judged clinical efficacy by three indicators, that is clinical symptoms, signs and laboratory examinations; Complete Remission (CR) means all three indicators improved completely; Partial Response (PR) means the patient's state of illness improved markedly, three indicators fully recovered or one incomplete recovery; Stable Disease (SD) means the condition improved after therapy and 2 or 3 of the indicators did not fully recover yet; Disease Progression (PD) means the condition did not improve significantly and even worsened; the clinical Response Rate (RR)=(CR+PR+SD)/cases×100 %. Adopted Statistical Package for the Social Sciences (SPSS) 26.0 software to analyze all data. Expressed count data by n % and tested by Chi-square (χ^2). Used to represent measurement data that conform to a normal distribution and t test to compare both groups; adopted paired t-test for the same group comparison before and after therapy. Adopted rank sum test to compare between groups. $p<0.05$, it indicated difference possessed statistical significance. Before treatment, compared both groups on serum creatinine, blood calcium and blood uric acid levels, they were of obvious divergence, it was of statistical significance ($p>0.05$); after 2 courses of treatment, compared both groups on serum creatinine, blood calcium and blood uric acid levels, observation group had bigger downtrend than control group, they had obvious differences, so it was of statistical significance ($p<0.05$) as shown in Table 1. Before treatment, compared both groups on serum Ig and light chain protein quantitative levels, they possessed no obvious divergence, it was statistically significant ($p>0.05$); after 2 courses of treatment, compared both groups on serum Ig and light chain protein quantitative levels, observation group had bigger downtrend than control group, they had obvious differences, so it was of statistical significance ($p<0.05$), as shown in Table 2. Adverse reactions rate in observation group (1 case infection, 2 cases nausea and vomiting, 3 cases dizziness and 1 case bone marrow suppression) was 17.5 %, but in control group (2 cases infection, 1 case nausea and vomiting, 3 cases dizziness and 2 cases bone marrow suppression) was 20.0 %, the difference was statistically significant ($p>0.05$), as shown in Table 3. After 2 courses of treatment, observation group (92.50 %) possessed higher total clinical efficacy than control group (82.50 %), they had obvious differences, so it was of statistical significance ($p<0.05$), as shown in Table 4. MM is a malignant tumor characterized by the clonal proliferation of terminally differentiated plasma cells in the bone marrow[10]. In the United States, MM accounts for 1 % to 18 % of all hematological malignancies, in 2018, estimated 30 770 new diagnoses and 12 770 deaths MM patients alone. MM causes the

secretion of nonfunctional monoclonal Ig produced by transformed plasma cells[11]. Abnormal Ig production can lead to multiple MM complications, such as renal insufficiency, neuropathy and hyper viscosity syndrome. However, MM with nephropathy will increase the clinical mortality of patients and the diversity of abnormal light chains produced by different myeloma clones determines the diversity of observed renal pathological damage, the potential of kidney disease is mainly divided into three forms namely tubular nephropathy in renal disease mediated by monoclonal Ig, Monoclonal Ig Deposition Disease (MIDD) and Amyloid Light (AL) chain amyloidosis[12]. Survival rates for myeloma are improving thanks to newer treatments, which also appear to improve outcomes for myeloma-related kidney injury[13]. Since monoclonal Ig-mediated kidney disease sometimes progresses rapidly and irreversibly, we should give fast-acting chemotherapeutics immediately after diagnosis. Total body treatment can prolong survival, even patients who rely on dialysis, some of them may recover kidney function after several months treatment[14]. Bortezomib, a proteasome inhibitor, is a powerful borate peptide small molecule, an important step forward in MM nephropathy treatment and an important drug that nephrologists should know about. Bortezomib and large dosage dexamethasone have been the most powerful therapies for treating myeloma related to severe AKI[15]. The efficacy and safety of bortezomib do not appear to be related to renal function and the drug takes effect quickly, with a median time to optimal response in clinical trials is only 30 d, it can effectively prevents permanent kidney damage, bortezomib's action mechanism has relationship with protein processing interference through the ubiquitin-proteasome pathway, it leads to malignant plasma cells apoptosis that synthesize large amounts of Ig[16]. Bortezomib restricts mitogen-activated kinase and Nuclear Factor kappa B (NF-κB) pathways, thereby destroying myeloma-stromal cell interactions, decreasing tumor neovascularization and increasing myeloma cell apoptosis[17]. By inhibiting these pathways, bortezomib also down regulates the inflammatory state induced by light chain processing in the proximal tubule and thus may reduce renal interstitial fibrosis development[18]. 40 % to 50 % of myeloma combined with AKI patients respond to the bortezomib regimen and their renal function will improve significantly within a few weeks. Lenalidomide, a novel treatment for myeloma patients, inhibits the growth of myeloma cells and disrupts the interaction between myeloma and bone marrow stromal cells, it needs to be used carefully in the presence of nephropathy and the dose must be reduced because it would be eliminated by the kidneys[19]. Nonetheless, it has no direct nephrotoxicity, therefore, an appropriate dose of lenalidomide is recommended for use. Our research is consistent with previous studies, showing that lenalidomide combined with bortezomib in MM nephropathy treatment can effectively improve renal function, reduce serum creatinine value, serum calcium and other indicators. There are also shortcomings in this study. At present, lenalidomide combined with bortezomib is still in the preliminary trial for MM nephropathy treatment, which drug has the greatest effect through what mechanism has not been experimentally confirmed and these issues need further investigations in the future and the small sample size of our study may also lead to biased results. However, this study also confirmed that lenalidomide combined with bortezomib in MM nephropathy treatment, observation group (92.50 %) possessed higher total clinical efficacy than control group (82.50 %) ($p<0.05$); observation group had smaller serum Ig, light chain protein quantitative levels, serum creatinine, blood calcium and blood uric acid drop than control group ($p<0.05$); observation group possessed 17.5 % adverse reactions rate, but control group 20.0 %, the divergence had no statistical significance ($p>0.05$). Lenalidomide combined with bortezomib in MM nephropathy treatment has better clinical efficacy; can effectively improve renal function and has greater clinical efficacy without increasing the incidence of adverse reactions, which is worthy of clinical application.

TABLE 1: COMPARISON OF RENAL FUNCTION INDEXES IN BOTH GROUPS BEFORE AND AFTER THERAPY ($\bar{x}\pm s$)

Item	Before and after treatment	Observation group (n=40)	Control group (n=40)	t	p
Serum creatinine (μmol/l)	Before treatment	1050.45±87.86	1053.57±90.95	0.33	0.75
	After treatment	201.23±8.67	252.68±9.47	3.57	0.007
Blood calcium (mmol/l)	Before treatment	5.61±0.53	5.52±0.61	0.35	0.71
	After treatment	2.81±0.39	4.37±0.61	9.35	0.000
Blood uric acid (μmol/l)	Before treatment	339.36±10.41	334.68±10.97	0.56	0.53
	After treatment	254.17±9.32	291.35±9.68	10.57	0.000

TABLE 2: COMPARISON OF SERUM IG AND LIGHT CHAIN PROTEIN QUANTITATIVE LEVELS BEFORE AND AFTER THERAPY BETWEEN BOTH GROUPS ($\bar{x}$±s)

Item	Before and after treatment	Observation group (n=40)	Control group (n=40)	t	p
Serum Ig (g/l)	Before treatment	34.45±4.58	33.87±4.37	0.28	0.74
	After treatment	16.18±2.35	26.18±3.67	9.46	0.001
Light chain protein quantitative levels (g/24 h)	Before treatment	3.58±0.34	3.52±0.36	0.47	0.71
	After treatment	1.57±0.43	2.32±0.56	7.02	0.002

TABLE 3: COMPARISON OF ADVERSE REACTIONS OCCURRENCE IN BOTH GROUPS BEFORE AND AFTER THERAPY

Group	Case	Infection	Nausea and vomiting	Dizziness	Bone marrow suppression	Total incidence (%)
Observation group	40	1	2	3	1	7 (17.5 %)
Control group	40	2	1	3	2	8 (20.0 %)
t				0.81		
p				0.068		

TABLE 4: COMPARISON OF CLINICAL EFFICACY IN BOTH GROUPS AFTER THERAPY

Group	CR	PR	SD	PD	Total clinical efficacy
Observation group	23 (57.5 %)	7 (17.50 %)	7 (17.50 %)	3 (7.50 %)	37 (92.50 %)
Control group	17(42.50 %)	8 (20.00 %)	8 (20.00 %)	7 (17.50 %)	33 (82.50 %)
χ^2			5.68		
p			0.002		

Conflict of interests:

The authors declared no conflict of interests.

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