Original Study

Pharmacokinetics and Safety of Elotuzumab Combined With Lenalidomide and Dexamethasone in Patients With Multiple Myeloma and Various Levels of Renal Impairment: Results of a Phase Ib Study

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Abstract

Renal impairment is associated with a poor prognosis in patients with multiple myeloma (MM), and more treatment options are needed. The pharmacokinetics of elotuzumab, a humanized IgG1 monoclonal antibody, combined with lenalidomide and dexamethasone, is not significantly different between patients with MM with and without renal impairment, suggesting that elotuzumab might be administered without dose adjustment for renal function.

Introduction: The present study evaluated the pharmacokinetics and safety of elotuzumab, a humanized IgG1 monoclonal antibody against signaling lymphocyte activation molecule-F7, combined with lenalidomide and dexamethasone, in patients with multiple myeloma (MM) and renal impairment. **Patients and Methods:** Patients with MM and normal renal function (NRF) (creatinine clearance [CrCl] $\geq$ 90 mL/min), severe renal impairment (SRI) (CrCl $<$ 30 mL/min, not requiring dialysis), or end-stage renal disease (ESRD) (requiring dialysis) were enrolled in this open-label, phase Ib study. Elotuzumab (10 mg/kg), lenalidomide (5-25 mg), and dexamethasone (40 mg) were administered in 28-day cycles until disease progression or unacceptable toxicity developed. The primary endpoint was single-dose elotuzumab pharmacokinetics. **Results:** A total of 26 patients (median age, 63 years) were treated (NRF, n = 8; SRI, n = 9; ESRD, n = 9). The median baseline CrCl was 105 mL/min (range, 84-146 mL/min) for those with NRF and 26 mL/min (range, 15-33 mL/min) for those with SRI. Twenty-three patients (89%) had received previous therapy (median, 2 regimens; range, 1-7). Treatment was discontinued in 6 patients with NRF, 4 with SRI, and 5 with ESRD, primarily because of disease progression. The mean elotuzumab serum concentrations were comparable across groups (n = 23). No statistically significant differences were observed in the maximum observed serum concentration, area under the concentration–time curve from time 0 to the last quantifiable serum concentration, or area under the concentration–time curve from time 0 to infinity when the SRI and ESRD groups were compared with the NRF group ($P > .05$). All patients had $\geq$ 1 adverse event (AE). Of the 8 patients with NRF, 9 with SRI, and 9 with ESRD, 7, 8, and 7 experienced grade 3 to 4 AEs. The overall response rates were 75% in the NRF, 67% in the SRI, and 56% in the ESRD groups. **Conclusion:** The results of the present study support the use of elotuzumab for the treatment of patients with MM and renal dysfunction without dose adjustment.

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Introduction

Renal impairment is a common comorbidity associated with multiple myeloma (MM), with ≤ 50% of patients affected during the course of their disease[1] and 10% requiring dialysis.[2] In most patients with MM, renal impairment is due to the overproduction of monoclonal free light chains, which causes cast nephropathy (also known as myeloma kidney).[1,3] Renal impairment is associated with poor outcomes[4] and is an important prognostic factor in MM. The median survival of patients with MM and renal failure has been reported to be 19.5 months compared with 40.4 months for patients without renal failure.[5] Furthermore, the reversal of renal impairment in patients with MM has been associated with an improved prognosis and longer overall survival (OS).[2,6]

Advances in therapy, including the use of immunomodulatory drugs (IMiDs) (eg, lenalidomide, thalidomide, and pomalidomide), proteasome inhibitors (eg, bortezomib), and autologous stem cell transplantation, have greatly improved the life expectancy of patients with MM, including those with impaired renal function.[7,8] Continuous lenalidomide and dexamethasone in newly diagnosed patients has demonstrated a median progression-free survival (PFS) of 25.5 months and an OS at 4 years of 59%.[9] The 1- and 3-year PFS have also been shown to be superior in patients newly treated with lenalidomide and dexamethasone compared with patients treated with placebo and dexamethasone (78% and 52% vs. 52% and 32%, respectively).[10] Furthermore, the overall response and very good partial response (VGPR) rates were 78% and 63% with lenalidomide and dexamethasone and 48% and 16% with placebo and dexamethasone, respectively. An overall response rate (ORR) of 64% was reported for patients with MM and impaired renal function treated with lenalidomide combined with high-dose dexamethasone, with improvements in renal function reported in 72% of patients with MM and mild-to-moderate renal impairment.[11] However, because lenalidomide is excreted primarily through the kidney, the half-life of the drug increases and drug clearance decreases linearly with the severity of kidney impairment. Thus, dose adjustments are required according to the creatinine clearance (CrCl).[11,12] Dimopoulos et al[11] reported that a dose reduction of lenalidomide or interruption because of adverse events (AEs) was necessary in 22% of patients with MM and mild or no renal impairment, 40% of patients with MM and moderate renal impairment, and 38% of patients with MM and severe renal impairment (SRI). Furthermore, patients with SRI treated with lenalidomide plus dexamethasone have been shown to have shorter OS compared with patients with mild or no renal impairment.[11] Also, the response rate has been shown to decline with severity of renal impairment.[13] To improve the outcome of patients with MM and renal impairment, new alternative efficacious and well-tolerated treatment options are necessary.

Elotuzumab is a humanized IgG1 immunostimulatory monoclonal antibody targeted against signaling lymphocyte activation molecule-F7 (SLAMF7; also referred to as CS1), a glycoprotein expressed on myeloma and natural killer cells but not on normal tissues.[14] Through both direct activation and engagement of natural killer cells, elotuzumab selectively targets and kills SLAMF7-expressing myeloma cells with minimal effects on normal tissue.[15] A phase I study assessing the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of elotuzumab (dose range, 0.5-20 mg/kg every 2 weeks) demonstrated that elotuzumab was generally well tolerated at doses sufficient to achieve consistent SLAMF7 saturation (10 or 20 mg/kg).[16] No objective responses were seen in this single-agent phase I trial. However, 27% of patients achieved disease stabilization. A phase Ib-II study investigating the safety and efficacy of elotuzumab combined with lenalidomide and dexamethasone demonstrated an ORR of 82% in phase Ib,[17] which compared favorably with the historical response rate of 60% with lenalidomide and dexamethasone alone in patients with relapsed or refractory MM (RRMM).[18,19] Moreover, in phase II of the study, an ORR of 84% and PFS of 29 months were observed, and treatment was generally well tolerated, with no dose-limiting toxicities reported.[20] In the randomized, open-label phase III ELOQUENT-2 study, patients treated with elotuzumab plus lenalidomide and dexamethasone demonstrated an ORR of 79% compared with an ORR of 66% for patients treated with lenalidomide and dexamethasone. A median PFS of 19.4 months versus 14.9 months was observed in the elotuzumab arm and lenalidomide/dexamethasone arm, respectively.[21] Bortezomib significantly enhanced elotuzumab activity in a preclinical model,[22] and a phase II, randomized, proof-of-concept study demonstrated a median PFS of 9.7 months for patients receiving elotuzumab combined with bortezomib and dexamethasone versus 6.9 months for patients receiving bortezomib and dexamethasone.[23]

To determine whether elotuzumab could be safely administered with lenalidomide and dexamethasone in patients with renal impairment, the present phase Ib study was conducted to evaluate the PK and safety of elotuzumab combined with lenalidomide and dexamethasone in patients with MM and various levels of renal function (normal renal function [NRF], SRI, and end-stage renal disease [ESRD]).

Patients and Methods

Study Design

The present study was a phase Ib, multicenter, open-label study (ClinicalTrials.gov identifier, NCT01393964) of elotuzumab combined with lenalidomide and dexamethasone in patients with MM and NRF (CrCl ≥ 90 mL/min), SRI (CrCl < 30 mL/min and not requiring dialysis), and ESRD (requiring dialysis). The present study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, and the ethical principles of the European Union Directive and the US Code of Federal Regulations. All patients (or, where necessary, legal guardians) provided written, informed consent before participation. The present study was conducted at 8 sites across the United States, with patients enrolled from January 2012 to October 2013. The cutoff for data analysis was June 30, 2014.

Treatment was administered in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. The overall study design is shown in Figure 1. During each cycle, elotuzumab