A Phase II Trial of TBL 12 Sea Cucumber Extract in Patients with Untreated Asymptomatic Myeloma

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Abstract

Sphingolipids/glycosides contained in sea cucumbers have been shown preclinically to have a number of antitumor properties, including the inhibition of osteoclastogenesis. In this pilot phase II trial, a total of 20 patients with high risk asymptomatic multiple myeloma (ASxMM) were given 40 ml of the sea cucumber abstract TBL12 twice daily.

The best response observed to date is a minimal response. A total of 9 patients remain on treatment having completed a median of 27 monthly cycles of TBL12 (range 24-33). The median progression free survival by Kaplan-Meyer analysis has not been reached. 8 patients came off study for PD after a median of 7.5 cycles for hypercalcemia (n=1), acute renal insufficiency (n=1), anemia (n=2), and for a new bony lesion on MRI (n=1). TBL12 was well tolerated with grade 1 nausea being the only toxicity observed. An SAE of pneumococcal pneumonia was felt to be unrelated.

The expected rate of progression of ASxMM at 2 years is 52% whereas the median PFS has not been reached in our study. This finding along with the fact that only 1 patient progressed by bone disease warrants further studies of TBL12 in ASxMM.

Background

Patients with smoldering multiple myeloma (MM) may remain asymptomatic (ASx) for variable amounts of time and are therefore typically monitored without treatment. Chemoprevention trials using thalidomide have found the toxicity to be prohibitive and longer follow up is needed for the early systemic treatment with lenalidomide and dexamethasone of high risk ASxMM (Mateos et al, ASH 2009). Of note, 10 of 21 subjects receiving placebo progressed due to bone disease in this lenalidomide versus placebo phase III study.

Based on encouraging preclinical data with bioactive food supplements in MM curcumin (Bharti et al., Blood 2003), resveratrol (Bhardwaj et al, Blood 2006), and a component of green tea extract (Shammas et al, Blood 2006) many patients are already using these agents without definitive proof of efficacy or safety.

The sphingolipids/glycosides contained in sea cucumbers have also been shown preclinically to have a number of antitumor properties including antiangiogenesis, direct tumor cytotoxicity, and also of particular relevance to MM, the inhibition of osteoclastogenesis (Kariya et al, Carb Res 2004).

TBL12, an extract of sea cucumber, has been commercially available since 1981 and used by human subjects as a food supplement without any reported toxicities. We therefore designed a pilot phase II study to determine the safety and efficacy of TBL12 in patients with ASxMM and here we present the updated data.

Objective

To determine the safety and efficacy of the sea cucumber extract TBL12 in patients with asymptomatic multiple myeloma.

Methods

Patients were required to have ASxMM with measurable disease, defined as:
- m-spike on serum electrophoresis of ≥ 1 g/dL and/or
- urine m spike of ≥ 200 mg/24 hours
- If non-secretory, then abnormal free light chains (FLC) were required.

A total of 20 patients with ASxMM were given open label TBL12, formulated as a liquid gel (manufactured by Unicorn Pacific Corporation, IND 103,543) to be kept frozen until the time of consumption.

Patients ingested 2 units of 20 ml twice per day, for a total of 80 ml per day. Disease parameters were monitored monthly and treatment was continued until disease progression.

Table 1 : Baseline Characteristics of Patients

Subject	Serum M-spike	BJP	Involved Ig	Involved FLC	K/L ratio	BM Bx % Plasma Cells	Immuno paresis
001	3.92	0	4891	243.4	332	50	2
002	3.8	0.08	4669	15.9	22.7	90	2
003	4.22	0.61	4808	654.2	86	30	2
004	3.34	0.01	3747	7.4	8.22	40	2
005	1.86	0.11	2478	60.3	0.088	10	2
006	4.34	0	3204	304.3	0.027	70	2
007	4.22	0.09	5647	618.3	476	60	2
008	0	0.05	567	1266.2	1055	55	2
009	3.73	0.02	6127	141	0.004	55	2
010	0	9.2	n/a	15962	53	25	2
011	2.35	0.03	2489	633.9	588	20	2
012	2.19	0.41	2673	8650	"High"	50	2
013	3.29	0	4736	4	5.22	49	2
014	3.81	0.03	5370	73	0.071	30	1
015	3.02	0.64	4311	517.5	75	36	2
016	4.42	0.08	6719	416.5	617	18	2
017	3.31	0.02	4359	909.2	0.007	25	1
018	3.48	0	4603	78	38	9 (24 on aspirate)	1
019	4.63	0.27	5826	472.9	430	70	2
020	2.35	0	1791	461.2	307	30	2

Results

23 patients were screened, with 3 failures, and the remaining 20 patients proceeded with study treatment. The median age of the patient was 58 years (range 22-75), with 11 males and 9 females. The phenotypes were 14 IgG, 5 Ig A, and one kappa light chain.

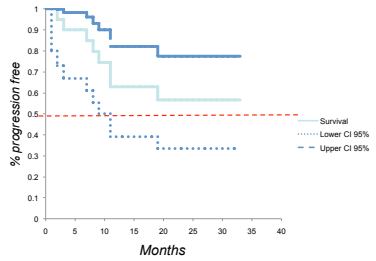
Baseline characteristics of the patients are shown in Table 1. Generally, this was a population at high risk for progression of disease (PD), with 14 patients having a serum m spike ≥ 3 g/dl and bone marrow plasma cells (BM PC) ≥ 10%. The median BM PC for all patients was 38% (range 10 to 90). (With the additional high risk criteria of a FLC ratio <0.125 or >8, 13 patients were high risk.) Of the remaining 6 patients, all had immunoparesis and 4 had markedly elevated FLC ratios (range 307-incalculable) and the remaining 2 patients had 9.2 g urine m spike and an IgA phenotype. Of note, the median time between initial diagnosis of ASxMM to the start of TBL12 treatment was 33 months (range 1-67).

Compliance was excellent and the treatment was well tolerated with only grade 1 nausea. There was one SAE, a pneumococcal pneumonia requiring admission, which was felt to be unrelated to study treatment. A total of 9 patients remain on treatment (including one with 70% plasma cell at baseline), having completed a median of 27 monthly cycles of TBL12 (range 24-33 cycles).

The median progression free survival (PFS) has not been reached by Kaplan-Meyer survival analysis (see Figure 1). The best response to date has been a minimal response (MR) for 5 cycles.

3 patients are on intermittent bisphosphonates therapy q 3-12 months for osteoporosis or equivocal bone lesions unchanged since screening.

Figure 1: Progression Free Survival



Results (continued)

8 patients came off study for PD after a median of 7.5 cycles (range 2-18). The reasons for PD include:
- 1 hypercalcemia,
- 1 acute renal insufficiency (after 2 cycles with 9.2g urine m spike at screening)
- 2 for anemia (one after 3 cycles with 90% BM PC at screening),
- and 1 for a new bony lesion on MRI.

2 patients withdrew consent after cycle 6 and 8 and
1 was removed after cycle 13 due to investigator discretion after the pneumococcal pneumonia SAE.

Conclusions

In this pilot study of high risk ASxMM patients, TBL12 is well tolerated and 9 (45%) patients remain on treatment with one MR noted. The expected rate of PD for high risk ASxMM is 52% at 2 years (Dispenzieri et al, Blood 2008) and to date, median PFS has not been reached in this study. Also, of note, in contrast to 10 of 21 pts in the placebo arm of lenalidomide in ASxMM study developing bone PD (Mateos et al, ASH 2010), only 1 patient in this study has bone PD. This may reflect anti-osteoclastogenesis effects of TBL12 observed in vitro and selective use of intravenous bisphosphonates in 3 patients. Further studies are required.

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Conflicts of Interest

There are no relevant conflicts of interest to disclose.