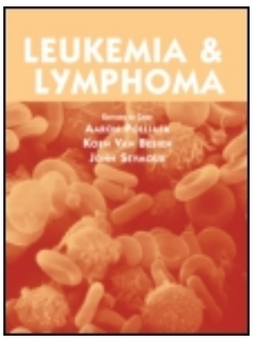

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Phase III randomised study of dexamethasone with or without oblimersen sodium for patients with advanced multiple myeloma

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Abstract

Upregulation of the Bcl-2 antiapoptotic protein is reported to be associated with aggressive clinical course in multiple myeloma. Oblimersen sodium is a *bcl-2* antisense oligonucleotide complementary to the first six codons of the open-reading frame of *bcl-2* mRNA that can decrease transcription of Bcl-2 protein and increase myeloma cell susceptibility to cytotoxic agents. In this phase III randomised trial, we investigated in patients with relapsed/refractory myeloma whether addition of oblimersen to dexamethasone improved clinical outcomes *vs*. dexamethasone alone. Two hundred and twenty-four patients were randomised to receive either oblimersen/dexamethasone ($N = 110$) or dexamethasone alone ($N = 114$). The primary endpoint was time to tumor progression (TTP). Final results of this study demonstrated no significant differences between the two groups in TTP or objective response rate. The oblimersen/dexamethasone regimen was generally well tolerated with fatigue, fever and nausea, the most common adverse events reported.

Keywords: *Multiple myeloma, Bcl-2 antisense, G3139, Genasense®, oblimersen*

Introduction

Dexamethasone is an important therapeutic agent for patients with multiple myeloma. Despite high initial response rates, complete responses are few and eventually all patients develop resistance, resulting in a compromised median survival of 2–3 years [1]. Bcl-2, an anti-apoptotic member of the Bcl-2 family of proteins that regulate mitochondria-mediated apoptosis, has been shown to be a key factor in chemotherapy resistance. It is over-expressed in many cancers [2,3], including multiple myeloma [4]. This over-expression shifts the balance of pro-apoptotic and anti-apoptotic proteins in favour of the latter, thereby preventing apoptosis induced by a wide variety of cell death stimuli, including chemotherapeutic agents, antitumor antibodies and radiation [5,6].

Evidence for the role of Bcl-2 in the development of resistance to chemotherapy in multiple myeloma has been found in a variety of studies. Several groups have shown that over-expression of Bcl-2 in multiple myeloma cells confers resistance to dexamethasone [7–11] and paclitaxel [12]. However,

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Bcl-2 over-expression does not result in resistance to melphalan or gemcitabine, drugs which induce apoptosis through a separate pathway [9,12].

Theoretically, any agent that interferes with Bcl-2 expression can increase chemotherapy sensitivity and/or reverse resistance to therapy, enhancing the ability of cytotoxic drugs such as dexamethasone to cause cell death [5]. One means of inhibiting Bcl-2 is through the use of antisense therapy to down-regulate *bcl-2* mRNA, thereby decreasing levels of Bcl-2 protein. Oblimersen sodium is a *bcl-2* antisense oligonucleotide that is complementary to the first six codons of the open-reading frame of *bcl-2* mRNA. It forms an aberrant heteroduplex with *bcl-2* mRNA that is detected and cleaved by RNAse-H, resulting in the degradation of *bcl-2* mRNA and decreased translation of the Bcl-2 protein [6,13]. Preclinically in myeloma cells, oblimersen is reported to decrease *bcl-2* mRNA levels and significantly enhance susceptibility to dexamethasone- and doxorubicin-induced apoptosis [14].

The preclinical evidence that Bcl-2 over-expression in myeloma cells confers resistance to dexamethasone and that oblimersen can down-regulate Bcl-2 protein levels and enhance susceptibility to dexamethasone prompted us to investigate oblimersen in multiple myeloma. The clinical trial reported here was undertaken to determine the role of oblimersen in combination with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma.

Patients and methods

This was a Phase III, multicentre, randomised, open-label, parallel-group study designed to evaluate whether the addition of oblimersen sodium to dexamethasone improved clinical outcomes over that of dexamethasone alone in patients with relapsed/refractory multiple myeloma.

The primary objective was to compare time to tumor progression (TTP) in the two groups. Key secondary objectives included a comparison of the treatment groups with respect to objective response rate, duration of response among responding patients and survival.

The study was conducted in accordance with applicable requirements regarding ethical review and informed consent, including those in the Declaration of Helsinki.

Key inclusion/exclusion criteria

Patients enrolled with multiple myeloma were to have relapsed after achieving at least a partial response to prior therapy or were to have refractory disease (i.e. primary resistance/progressive disease after achieving less than a partial response following treatment with $\geq$two cycles of chemotherapy [including at least one myelosuppressive drug]) within the 3 months prior to randomisation or progressive disease after high-dose chemotherapy and autologous stem cell transplantation. Patients also had to have measurable disease as determined by serum M protein level >1.0 g/dL (measured by serum protein electrophoresis) or urine M protein excretion >200 mg in 24 h.

Other requirements included bone marrow plasmacytosis with $>5\%$ total nucleated cells; prothrombin time (PT) <1.5 times the upper limit of normal ($\times$ULN) and partial thromboplastin time $<1.5 \times$ULN; creatinine ≤ 1.5 mg/dL; absolute neutrophil count $>1000/\mu$L; platelets $\geq 50\,000/\mu$L; and ECOG performance status 0–3. Patients were excluded if they had >6 prior treatment regimens, a previous allogeneic stem cell transplant or a history of renal dialysis or other significant medical disease.

Stratification and randomisation

Eligible patients were stratified according to three parameters: relapse after response *vs*. primary resistance to treatment; prior *vs*. no prior autologous stem cell transplantation and one to two prior treatment regimens *vs*. three to six prior treatment regimens. Following stratification, they were centrally randomised via an interactive voice response system in a 1:1 ratio to treatment with oblimersen plus dexamethasone or dexamethasone alone.

Treatment protocol

Treatment was administered in two phases: the induction period (cycle 1) and the retreatment period (cycles subsequent to cycle 1). *Cycle 1:* during the 28-day induction period, patients in the oblimersen/dexamethasone group received oblimersen 7 mg/kg/day by continuous intravenous infusion for 7 consecutive days (days 1–7) during each of weeks 1 and 3 and dexamethasone 40 mg orally on days 4, 5, 6 and 7 during each of weeks 1, 2 and 3. Patients in the dexamethasone only group received dexamethasone 40 mg orally on days 1, 2, 3 and 4 during each of weeks 1, 2 and 3. No treatment was given during week 4 to patients in either group. *Cycles subsequent to cycle 1*: patients in the combination arm received oblimersen 7 mg/kg/day by continuous infusion for seven consecutive days (days 1–7) and dexamethasone 40 mg orally on days 4, 5, 6 and 7 during week 1. Patients in the dexamethasone only group received dexamethasone 40 mg orally on days 1, 2, 3 and 4 during week 1. No treatment was given during

weeks 2 and 3 to patients in either group. Retreatment cycles were repeated every 3 weeks for a maximum of 1 year in patients who had stable or responsive disease and who tolerated therapy. *Prophylaxis:* All patients received concomitant prophylactic treatment with antibiotics, histamine-receptor antagonists and pamidronate or zoledronic acid.

Efficacy and safety evaluations and endpoints

Efficacy and safety evaluations were performed on day 15 and at the end of the induction period (i.e. week 4), 7 days before each retreatment cycle, and within 4 weeks after withdrawal from the study. Patients were followed every 2 months for up to 2 years from the date of last dose of study medication.

The primary endpoint of this study was TTP, which was calculated from the date of randomisation to the date of progression and was determined based on blinded clinical expert review by S. Jagannath (St. Vincent's Comprehensive Cancer Centre, New York, NY) and M Oken (Hubert H. Humphrey Cancer Centre, Robbinsdale, MN). Progression was defined as the first of the following events to occur prior to initiation of non-study myeloma therapy: objective documentation of progressive disease, death within 60 days of the last evaluation of objective response status or death within 60 days of the last dose if there was no evaluation of objective response status.

Key secondary endpoints included objective response rate (i.e. complete response, response [75% improvement] or partial response as assessed by the investigator according to criteria adapted from SWOG [15]) and overall survival.

Statistical methods

A sample of 200 patients (100 per treatment arm) was required to provide an 80% power to detect a significant difference between treatment groups with respect to TTP. This sample size was based on the following assumptions: distributions of TTP for the two treatment groups would be compared using the log-rank test with a two-sided significance level of 0.05; median TTP would be 4 months for patients who received dexamethasone alone and 6.33 months for patients who received oblimersen plus dexamethasone; equal numbers of patients would be assigned to each treatment arm and would be accrued over 12 months (approximately 18 per month) with a 6-month follow-up period after enrolment of the last patient; and the final analysis would be performed 1 year after the enrolment of the last patient. The sample estimate was obtained by using the EaSt Computer Software Package by Cytel. No interim analysis was performed.

The primary efficacy analysis was a comparison of the distributions of TTP between the two treatment groups in the intent-to-treat (ITT) population using the log-rank test. The Cox proportional hazards model with a covariate for treatment was used to estimate the hazard ratio for TTP.

With respect to key secondary endpoints, Fisher's exact test was used to compare the proportion of patients with objective response in the two treatment groups, and the odds ratio and exact 95% confidence interval also were provided for this endpoint. Survival time was calculated from the date of randomisation to the date of death. The primary analysis of survival was to occur when all patients had been followed for 2 years after the end of treatment.

Results

Patients

A total of 224 patients comprising the ITT population were enrolled at 78 sites in four countries (72 sites in the United States, 4 in Canada and 1 each in England and France). The first patient was enrolled in March 2001 and the last in April 2003.

One hundred ten patients were randomised to receive oblimersen/dexamethasone and 114 to dexamethasone alone. Four patients in each group were randomised but did not initiate treatment; thus, the safety population was composed of the 216 patients who received treatment (106 in the oblimersen/dexamethasone group and 110 in the dexamethasone group). The distribution of patients enrolled by stratum was similar in both treatment arms.

At baseline, an imbalance was observed between the treatment groups in several important prognostic factors (Table I). ECOG performance status at baseline was significantly worse in the oblimersen/dexamethasone group ($p = 0.028$). In addition, more patients in the oblimersen/dexamethasone group had stage III disease than in the dexamethasone group (70% *vs.* 61%, respectively). Also, imbalances in baseline laboratory parameters revealed that patients in the oblimersen/dexamethasone group were more seriously impaired than those in the dexamethasone group (serum creatinine >2.0 mg/dL: 5% and 0%, respectively [$p = 0.021$]; and elevated lactate dehydrogenase: 23% and 11%, respectively [$p = 0.025$]).

Patients in both groups had been heavily pretreated; the median number of prior regimens was 3 in both treatment groups. A total of 87 (79%) patients in the oblimersen/dexamethasone group and 95 (83%) patients in the dexamethasone group had been previously treated with dexamethasone; 47 and

51 of these patients, respectively, had been refractory to that treatment, achieving a response not better than stable disease.

Table I. Patient demographics, disease characteristics and treatment history.

Characteristic	Oblimersen/ dexamethasone ($N=110$)	Dexamethasone ($N=114$)	*p*-value
Age			
Mean/median	60/59	63/65	0.035
<65 years, *n* (%)	66 (60)	55 (48)	
Male/female, *n*/*n*	58/52	64/50	
Race, *n* (%)			
White/not Hispanic	74 (67)	91 (80)	0.019
Black/not Hispanic	24 (22)	11 (10)	
Hispanic	9 (8)	12 (11)	
Asian/Pacific Islander	3 (3)	0 (0)	
ECOG performance status			
Median [range]	1 [0–3]	1 [0–2]	0.028
0, *n* (%)	31 (28)	44 (39)	
1, *n* (%)	63 (57)	63 (55)	
2, *n* (%)	14 (13)	7 (6)	
3, *n* (%)	2 (2)	0 (0)	
Serum β_2-microglobulin, *n* (5)			
≥4 mg/L	52 (47)	41 (36)	0.083
<4 mg/L	56 (51)	71 (62)	
Subtype, *n* (%)			
IgG	62 (56)	67 (59)	>0.10
IgA	22 (20)	23 (20)	
IgM	0 (0)	1 (1)	
Other	26 (24)	23 (20)	
Durie-Salmon stage, *n* (%)			
I	8 (7)	11 (10)	>0.10
II	25 (23)	32 (28)	
III	77 (70)	70 (61)	
Unknown	0 (0)	1 (1)	
Time from diagnosis, months			
Median [range]	32 [5–185]	33 [7–232]	>0.10
Number of prior regimens, *n* (%)			
1–2	48 (44)	43 (38)	>0.10
>3	62 (56)	71 (62)	
Baseline LDH			
Normal	69 (62.7)	83 (72.8)	0.025
Elevated	25 (22.7)	13 (11.4)	
Baseline creatinine, *n* (%)			
Creatinine ≤2.0 mg/dL	105 (95.5)	114 (100)	0.021
Creatinine >2.0 mg/dL	5 (4.5)	0 (0)	
Prior autologous stem cell transplant, *n* (%)	58 (53)	56 (49)	>0.10
Response to prior treatment, *n* (%)			
Primary refractory	30 (27)	31 (27)	>0.10
Relapsed	80 (73)	83 (73)	

Discontinuations

In the ITT population, 103 (94%) of the oblimersen/dexamethasone group and 94 (83%) of the dexamethasone group discontinued treatment, that is, initiated <16 cycles or received <1 year (defined as 335 days) of protocol-specified therapy from the date of first dose. Disease progression/lack of efficacy accounted for more than 50% of the discontinuations in each group (oblimersen/dexamethasone: 63%; dexamethasone: 55%). Adverse event/toxicity was the second most frequently cited reason for discontinuation in each group and was reported for 16% of patients in each group. Seven percent of the oblimersen/dexamethasone group and 4% of the dexamethasone group discontinued for other reasons, including proceeding to transplant, noncompliance or removal based on physician's request, and another 7% and 8%, respectively, either withdrew consent or failed to return.

Efficacy

No significant difference in TTP was observed between the oblimersen/dexamethasone arm and the dexamethasone arm (94 *vs.* 108 days, respectively; $p=0.26$) (Table II). The objective response rates in the two groups were also similar (15% *vs.* 17%, respectively) (Table III). There were no complete responses as defined based on the Bladé criteria, [16] and no differences were observed when findings were analysed by disease stage (results not shown). The study was terminated in 2004, and the follow-up of patients for up to 2 years after the end of treatment was not completed. Thus, the analysis of survival included data available through a cut-off date approximately 1 year after enrolment of the last subject and did not show an advantage of oblimersen/dexamethasone over standard therapy (55% *vs.* 42% of treated patients; $p=0.29$ based on logistic

Table II. Time to tumor progression: *intent-to-treat population.

	Oblimersen/ dexamethasone ($N=110$)	Dexamethasone ($N=114$)	Hazard ratio	*p*-value
Patients with progression, *n* (%)	85 (77)	86 (75)		
Time to progression (days)				
Median	94	108	1.07	0.26
95% CI	(72, 116)	(79, 167)	(0.88, 1.61)	

CI, confidence interval.
*Based on multivariate analysis that adjusted for baseline imbalances.

regression analysis after adjustment for baseline imbalances).

Safety

All treated patients in both groups had at least one adverse event. The most common adverse event in both treatment groups was fatigue, occurring in 54% of the patients receiving oblimersen/dexamethasone and 45% of those receiving dexamethasone. Other adverse events occurring in ≥25% of the patients in the oblimersen/dexamethasone group were fever (48%), nausea (41%), insomnia (35%), anemia (33%), arthralgia (31%), constipation (31%), diarrhea (27%) and vomiting (25%). In the dexamethasone group, insomnia (34%) and weakness (25%) were the only adverse events besides fatigue that occurred in ≥25% of patients (Table IV).

The percentage of patients who discontinued because of an adverse event was the same in both arms (16%); events that resulted in discontinuation and were considered to be treatment related were reported for 12% of patients in the oblimersen/dexamethasone group and 14% of patients in the dexamethasone group. In both groups, half of the patients who discontinued due to an adverse event did so in cycle 1. No single adverse event or cluster of adverse events resulted in cycle 1 discontinuations.

Renal and hematologic toxicities. An increase in blood creatinine was noted in 25% of the oblimersen/dexamethasone patients and 15% of the dexamethasone patients, and was Grade 3 or 4 in 8% and 4%, respectively (Table IV). In both treatment groups, increase in blood creatinine was more likely to occur in patients with elevated baseline serum creatinine (>1.5 mg/dL) and in patients who were black and/or had concurrent medical conditions that affect renal function, such as diabetes or hypertension. Despite the increased percentage of patients in the oblimersen/dexamethasone group with increased blood creatinine, the incidence of patients experiencing renal failure was comparable in the two groups (oblimersen/ dexamethasone: three [3%] patients; dexamethasone: four [4%] patients).

Table III. Objective response rate: intent-to-treat population.

	Oblimersen/dexamethasone ($N=110$), *n* (%)	Dexamethasone ($N=114$), *n* (%)	Odds ratio (95% CI)	*p*-value
Objective responders	16 (15)	19 (17)	0.85 (0.38, 1.87)	0.72
75% improvement	4 (4)	8 (7)		
Partial response	12 (11)	11 (10)		

CI, confidence interval.

Table IV. Frequently occurring adverse events: safety population.

	All		Grade 3/Grade 4	
Adverse event	Oblimersen/dexamethasone ($N=106$), %	Dexamethasone ($N=110$), %	Oblimersen/dexamethasone ($N=106$), %	Dexamethasone ($N=110$), %
Fatigue	54	45	12	4
Fever	48	15	7	1
Nausea	41	24	3	0
Insomnia	35	34	0	2
Anemia	33	23	12	12
Arthralgia	31	20	3	2
Constipation	31	13	2	0
Diarrhea	27	15	5	2
Vomiting	25	8	2	0
Increased blood creatinine	25	15	8	4
Bone pain	22	15	2	3
Cough	22	21	0	1
Thrombocytopenia	22	9	14	5
Headache	21	11	0	1
Weakness	15	25	1	3
Back pain	14	21	5	4
Peripheral edema	13	22	2	1

Includes adverse events (regardless of relationship to treatment) that occurred in ≥20% of patients in either treatment group.

Thrombocytopenia was observed in 22% of oblimersen/dexamethasone patients and 9% of dexamethasone patients and was Grade 3 or Grade 4 in 14% and 5%, respectively. The incidence of Grade 3 or 4 bleeding events was similar in the two treatment groups (6% and 5%, respectively). In both groups, the incidence of Grade 3 or Grade 4 anemia was 12% and the incidence of Grade 3 or Grade 4 neutropenia was 4%.

Deaths. The incidence of adverse events with an outcome of death during treatment or within 30 days of the end of treatment was similar in the two treatment groups (oblimersen/dexamethasone: 13 (12%); dexamethasone: 10 (9%) (Table V). Disease progression was the most frequently reported cause of death, accounting for five deaths in the combination arm and three deaths in the dexamethasone arm.

Discussion

New drug development remains a priority in multiple myeloma. Bcl-2 is an important target for this disease. This is the first randomised clinical trial of any antisense therapy in patients with multiple myeloma. Although preclinical [14] and two Phase II [17,18] studies of oblimersen in myeloma demonstrated promising results, the results of this study failed to demonstrate the superiority of the addition of oblimersen to dexamethasone over dexamethasone alone.

Several factors may account for the results reported here. One important factor may be the patient population studied. Patients enrolled in this trial had advanced aggressive disease, had received multiple prior therapies and were likely to be refractory to the standard treatment (dexamethasone). In fact, the dexamethasone group in our study reflects patients with more advanced stage of disease when compared with dexamethasone group in recently reported studies [19,20] in relapsed/refractory myeloma with a median time to progression of 108 days *vs*. 140 days, respectively.

As recently reported in patients with relapsed/refractory chronic lymphocytic leukemia, those who remained sensitive to fludarabine achieved the maximum benefit, including a survival benefit, with oblimersen in combination with fludarabine and cyclophosphamide [21] It is possible that at a later stage in the clinical course of multiple myeloma, Bcl-2 maybe a redundant pathway as a therapeutic target and the combination of oblimersen with dexamethasone may not be the most optimal strategy to target myeloma cells. A chemotherapy-based combination may be more clinically beneficial as noted in two Phase II studies [17,18] Another factor was the significant difference between treatment groups in baseline characteristics (including performance status, renal function and LDH) that favoured the dexamethasone arm. This imbalance in prognostic factors may have obscured the potential clinical benefit of oblimersen in this study.

Oblimersen was generally well tolerated. Despite an increased incidence of a number of adverse events in the oblimersen/dexamethasone group, the percentage of patients who discontinued treatment as a result was balanced (16%) in both groups. Of note, first-cycle cytokine release syndrome previously reported in patients with chronic lymphocytic leukemia [21,22] was not observed in any patient with myeloma treated with oblimersen whereas one patient who inadvertently received the full 7-days dose of oblimersen over 7 h did not have any toxicity.

This first randomised clinical trial investigating an antisense approach in myeloma failed to demonstrate a clinical benefit with oblimersen when combined with dexamethasone, despite promising preclinical and Phase II results. Because previous clinical investigations demonstrated that oblimersen can effectively down-regulate Bcl-2 protein *in vitro* and in tumor cells obtained from patients treated with oblimersen, the current study did not investigate this [18]. It is also conceivable that targeting Bcl-2 so late in the course of this disease may not be the most optimal strategy, as the interplay of several anti-apoptotic pathways in myeloma cells may override the benefit of targeting only one. Thus, it is possible that using oblimersen early on in the clinical course of disease may be a more effective approach

Table V. Adverse events with an outcome of death: safety population.

Adverse event	Oblimersen/dexamethasone ($N = 106$), *n* (%)	Dexamethasone ($N = 110$), *n* (%)
Had an event with outcome of death	13 (12)	10 (9)
Disease progression	5 (5)	3 (3)
Renal failure	1 (1)	1 (1)
Ventricular arrhythmia	1 (1)	1 (1)
Acute abdomen	1 (1)	0 (0)
Cardiac arrest	1 (1)	0 (0)
Hemorrhagic stroke	1 (1)	0 (0)
Intracranial hemorrhage	1 (1)	0 (0)
Pneumonia	1 (1)	0 (0)
Subdural hematoma	1 (1)	0 (0)
Congestive cardiac failure	0 (0)	1 (1)
Cardio-respiratory arrest	0 (0)	1 (1)
Gastrointestinal hemorrhage	0 (0)	1 (1)
Multi-organ failure	0 (0)	1 (1)
Streptococcal septicemia	0 (0)	1 (1)

warranting further investigation. Also, recent preclinical evaluation has demonstrated the potent antitumor effect of combining oblimersen with chemotherapeutics or novel agents such as bortezomib, [23] thus providing additional opportunity for clinical investigation.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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