Efficacy of Treatment with Antisense Oligonucleotides Complementary to Immunoglobulin Sequences of bcl-2/Immunoglobulin Fusion Transcript in a t(14;18) Human Lymphoma-scid Mouse Model

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ABSTRACT
In t(14;18)-positive lymphoma cells, bcl-2 is expressed from a fusion mRNA transcript containing the full coding sequence of bcl-2 and 3' immunoglobulin sequences. We previously reported that antisense oligodeoxynucleotides targeted at the bcl-2 translational start site, as well as those targeted to immunoglobulin sequences 3' of the transcriptional breakpoint, down-regulate bcl-2 and inhibit growth of the t(14;18)-positive lymphoma line WSU-FSCCL in vitro. We have developed a scid mouse model with this human cell line and demonstrate that antisense oligodeoxynucleotides targeted to immunoglobulin sequences downstream of the breakpoint prevent apoptosis and induce apoptosis of WSU-FSCCL cells in vivo. This leads to prolonged survival of the mice. Targeting non-oncogenic sequences outside of the breakpoints of fusion transcripts may be a clinically useful therapeutic strategy.

INTRODUCTION
Specific genetic abnormalities represent targets for novel therapeutic strategies of malignancies. The most common genetic abnormality in non-Hodgkin's lymphoma is the chromosomal translocation t(14;18)(q32;q21) (1). From this translocation, a fusion transcript is expressed that contains the entire bcl-2 coding sequence with a 3' breakpoint fused to the immunoglobulin C H region (1–4). Dereguulated expression of bcl-2 prevents apoptosis and thus contributes to lymphoma development. Antisense oligonucleotides targeted to bcl-2 sequences can down-regulate bcl-2 in vitro (5–10), in vivo in murine models (11–13), and in human trials (14). Although toxicity from bcl-2 down-regulation in normal tissues has not been observed as a major problem with short-term treatments in small numbers of patients (15), bcl-2 is expressed in a number of critical tissues (10, 16), and bcl-2 knockout mice have a range of abnormalities (15, 17). In attempting to design a specific method to down-regulate bcl-2 from the fusion transcript, we have targeted the immunoglobulin sequences fused to bcl-2 downstream of the breakpoint. We have reported (18) that AS3 oligonucleotides designed to bind to these 3' immunoglobulin sequences specifically down-regulate bcl-2 expression in vivo and induce apoptosis in t(14;18)-containing WSU-FSCCL cells. We have developed a scid mouse model to further investigate the potential clinical utility of these immunoglobulin-targeted oligonucleotides against follicular lymphoma cells.

MATERIALS AND METHODS
Cell Line. WSU-FSCCL cells were grown as described (6) and resuspended in PBS at a concentration of 5 × 10⁷ cells/ml, and 0.2 ml was injected/mouse. Routes of injection included i.p., via a tail vein, or s.c.

scid Mice. CB.17 scid mice were obtained from and housed in the Fox Chase Cancer Center Laboratory Animal Facility under an approved protocol. Mice used were females, 4–6 weeks of age, at the time of cell injection. Mice were checked daily by the laboratory animal facility staff and at least three times weekly by the investigators, per an approved animal use protocol. Mice were followed until death or, more usually, sacrificed by CO₂ inhalation when they appeared moribund or to be suffering.

Mice received injections of 1 × 10⁷ FSCCL cells i.p. For survival experiments, repetitive doses of 200 μg (~10 mg/kg) of the indicated oligonucleotide were added at the times indicated. For assays of bcl-2 protein levels or apoptosis, lymphoma cells were allowed to grow for 5 weeks. At that time, 200–400 μg of the indicated oligonucleotide were injected i.p. Where indicated, the caspase inhibitor, Z-VAD (Enzyme Systems Products, Livermore, CA) was injected i.p. at a dose of 500 mg/mouse.

The abbreviations used are: AS, antisense; scid, severe combined immunodeficient; Z-VAD, Z-Val-Ala-Asp; PE, phyceroerythrin.
Flow Cytometry. Ascites or single-cell suspensions of spleen were suspended in PBSF (PBS containing 2.5% fetal bovine serum and 0.01% sodium azide). These were pelleted, washed once with PBS + 0.01% sodium azide, and then resuspended in the same solution. Cells in 100 μl were incubated with 20 μl of R-PE-conjugated antibody to CD38 or CD45 or to the negative control R-PE-IgG (PharMingen, San Diego, CA) for 30 min in the dark at 4°C. Cells were then washed in PBSF and once in PBS + 0.01% sodium azide. Cells were then fixed and permeabilized in 500 μl of 1.0% paraformaldehyde and 0.1% saponin (Sigma Chemical Co., St. Louis, MO) in the dark for 15 min at room temperature and washed twice in PBS + 0.1% sodium azide. Fifty μl of protein block serum-free (DAKO, Carpinteria, CA) and 50 μl of 0.1% saponin in PBS-azide were added to the pellet, gently vortexed, and incubated with 10 μl of FITC-anti bcl-2 antibody or FITC-conjugated negative control IgG antibody (DAKO) for 30 min in the dark at 4°C. Cells were washed twice in PBS-azide and resuspended in 300 μl of PBS-azide. Analysis was on a FACSscan.

Apoptosis. Apoptosis was assayed by use of APO 2.7 (Coulter). Cells were collected, washed in PBSF, and resuspended in 100 μl of cold PBSF + 0.1% digitonin (Sigma) for 20 min on ice. Cells were then washed in PBSF and pelleted. The cell pellet was resuspended in 80 μl of APO 2.7-labeled with PE-Cy5 or control PE-IgG for 15 min at room temperature. Cells were washed in PBSF, resuspended in 0.5 ml of PBSF, and analyzed on a FACSscan.

Western Blot. Single-cell suspensions of spleen or ascites were washed three times in PBS-azide. Cells were lysed at 30 μl of RIPA containing 100 μg/ml PMSF and 1 μg/ml aprotinin and incubated on ice for 30 min, followed by centrifugation at 1200 × g for 15 min at 4°C. The supernatant was removed and separated on 12% SDS-PAGE gels (Tris-HCl Ready-Gel; Bio-Rad, Hercules, CA). Transfer was to Immobilon-P membrane (Millipore, Bedford, MA), as suggested by the manufacturer. To the preblocked membrane, monoclonal mouse anti-bcl-2 antibody (clone bcl-2–100; Zymed Laboratories, Inc., South San Francisco, CA) was added at a 1:3000 dilution as the secondary antibody for 30 min. Bands were detected by chemiluminescence (ECL) after exposure to Hyperfilm ECL (Amersham). Blots were stripped with 0.2 NaOH, blocked, and reprobed with unconjugated antibody to human CD38 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA) at 1:1600 concentration for 1 h. Detection was as described above. Images from the X-ray films were scanned on a UMAX Vista-S6E scanner using V-scan 2.4.3 software on a Macintosh computer. The intensity of each band was analyzed by NIH image 1.61 software.

Oligonucleotides. Fully phosphorothioate-modified oligonucleotides were synthesized at the Fox Chase Cancer Center Macromolecular Core Facility. Sequences of oligonucleotides (5’-3’) were: BCL-2 AS, gtcttccacgtgcgc (19); BCL-2 mut, tggcgcctggctgcgc (6); cμ AS, gaagacgctcacttggt (20); and cμ mut, gtacagctcacttggtgc. The mutated sequences have eight base changes that retain the same overall number of adenine, thymine, guanine, and cytosine bases. Murine cμ is: gaacacatattcattgg (21).

RESULTS

Establishment of the WSU-FSCCL-scid Model. For reproducible growth of WSU-FSCCL cells in scid mice, the mice were initially preconditioned with cyclophosphamide. Once the cells were passaged through the mice, however, they grew without such preconditioning. These cells could then be taken from the mice, maintained in cell culture, and still grow when re injected into non-preconditioned scid mice. Whether cells were injected i.p., s.c., or i.v. did not alter the development of generalized lymphoma characterized by retroperitoneal and mesenteric adenopathy and infiltration of the liver, spleen, and marrow. Occasionally, a localized tumor developed after s.c. injection, but this was not observed consistently. After i.p. injection, ascites and mesenteric adenopathy were more prominent. Because discrete measurable tumors did not consistently develop with any of these methods of injection, survival was used as the endpoint for efficacy of treatment. For ease of administration, the i.p. route was used for these experiments.

After i.p. injection of 1 × 107 cells into CB.17 scid mice, 4–6 weeks of age, animals became visibly ill at 6–8 weeks and died or were euthanized at 8–11 weeks. At necropsy, the mice had lymphomatous ascites, splenomegaly, and bulky mesenteric and retroperitoneal adenopathy. Microscopically, spleen and marrow were replaced by lymphoma, whereas the liver revealed periportal infiltration with lymphoma. Kidneys were encased by, but not infiltrated with, lymphoma. Mice that survived longer because of treatment (see below) did develop meningeal involvement as well.

The lymphoma that developed in vivo closely recapitulated the characteristics of the cell line. The growth pattern was vaguely follicular. By flow cytometry, the lymphoma consisted of CD10+ B cells expressing CD19 and CD20. CD38 and CD45, but not CD5, CD23, or FMC7, were expressed. The major differences between the cell line in vitro and the lymphoma in vivo were that, in the mice, surface κ light chain became very faint, CD20 expression was less intense, and cell size was larger. By immunohistochemistry, bcl-2 and CD20 were positive.

Efficacy of cμ Antisense Oligonucleotides. As an initial test of in vivo efficacy of AS oligonucleotides targeted to the immunoglobulin portion of the bcl-2-immunoglobulin fusion transcript, we examined ascites before and after i.p. injections of the oligonucleotides. Five weeks after injection, human cells grew without such preconditioning. These cells could then be taken from the mice, maintained in cell culture, and still grow when re injected into non-preconditioned scid mice. Whether cells were injected i.p., s.c., or i.v. did not alter the development of generalized lymphoma characterized by retroperitoneal and mesenteric adenopathy and infiltration of the liver, spleen, and marrow. Occasionally, a localized tumor developed after s.c. injection, but this was not observed consistently. After i.p. injection, ascites and mesenteric adenopathy were more prominent. Because discrete measurable tumors did not consistently develop with any of these methods of injection, survival was used as the endpoint for efficacy of treatment. For ease of administration, the i.p. route was used for these experiments.

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Induction of Apoptosis by cμ Antisense Oligonucleotides. Down-regulation of the antiapoptotic bcl-2 protein is predicted to induce apoptosis. Mice inoculated with WSU-FSCCL cells 5 weeks previously were treated with 200 μg (10
mg/kg) of c<sub>m</sub>-AS oligonucleotide or mutated control, as in Fig. 1, and ascites specimens were analyzed. Apoptotic cells were visible in cytospin preparations at 8 h. To quantitate the effect, we used an antibody (Apo 2.7) to a mitochondrial membrane protein that is involved in apoptosis and detected on the surface of early apoptotic cells. Background apoptosis in cells from untreated mice is 1–3%. Increased apoptosis was detected within 4 h after oligonucleotide injection, peaked at 16 h, and was returning to baseline by 24 h (not shown). We postulated that if bcl-2 down-regulation and apoptosis were temporally closely linked, then it would be difficult to detect cells that had low bcl-2 expression but had not undergone apoptosis. Thus, if cells could be trapped in a bcl-2<sub>low</sub> state by inhibiting apoptosis, then the specific down-regulation of bcl-2 could be demonstrated. Accordingly, mice were inoculated with WSU-FSCCL cells and treated 5 weeks later with 400 μg i.p. of AS or mutated c<sub>m</sub>-oligonucleotide. The caspase inhibitor Z-VAD was administered i.p. 2 h later to block apoptosis. Spleens were removed 8 h after oligonucleotide treatment, and bcl-2 protein levels were assayed relative to human CD38 expression by Western analysis. A representative blot is shown (Fig. 3). In three experiments, each with two animals/experiment, densitometric analysis of the blots revealed that the ratio of bcl-2:CD38 in the presence of Z-VAD was 110.8 ± 22.9 with the control oligonucleotide treatment versus 17.8 ± 35.5 for AS c<sub>m</sub>-treated mice.

Fig. 1 Flow cytometric analysis of ascites. WSU-FSCCL cells were injected i.p. and allowed to grow for 5 weeks. AS-c<sub>m</sub> oligonucleotides or control (Mutant) oligonucleotides (200 μg) were injected i.p., and ascites were removed on day 0, 2, 4, or 7. Cells were stained for bcl-2 (X axis) and CD38 (Y axis). Only a lack of effect on day 2 is shown for the mutant oligonucleotides.

Down-Regulation of bcl-2 Protein by c<sub>n</sub> AS Oligonucleotides. We have reported that bcl-2 is down-regulated in WSU-FSCCL cells in vitro by c<sub>n</sub> AS oligonucleotides (18). Our initial attempts to similarly confirm down-regulation in vivo were unsuccessful. Because of the reported bcl-2 half-life of >10 h (5), we had initially examined later time points. By then, however, many cells were already apoptotic. Because the peak of apoptosis is at 16 h, earlier time points were examined. At 8 h, bcl-2 was variably down-regulated in spleen tissue. We postulated that if bcl-2 down-regulation and apoptosis were temporally closely linked, then it would be difficult to detect cells that had low bcl-2 expression but had not undergone apoptosis. Thus, if cells could be trapped in a bcl-2<sub>low</sub> state by inhibiting apoptosis, then the specific down-regulation of bcl-2 could be demonstrated. Accordingly, mice were inoculated with WSU-FSCCL cells and treated 5 weeks later with 400 μg i.p. of AS or mutated c<sub>n</sub> oligonucleotide. The caspase inhibitor Z-VAD was administered i.p. 2 h later to block apoptosis. Spleens were removed 8 h after oligonucleotide treatment, and bcl-2 protein levels were assayed relative to human CD38 expression by Western analysis. A representative blot is shown (Fig. 3). In three experiments, each with two animals/experiment, densitometric analysis of the blots revealed that the ratio of bcl-2:CD38 in the presence of Z-VAD was 110.8 ± 22.9 with the control oligonucleotide treatment versus 17.8 ± 35.5 for AS c<sub>n</sub>-treated mice.

We used flow cytometric detection of bcl-2 as an alternative method of demonstrating and quantifying bcl-2 down-regulation in human CD45<sup>+</sup> cells in spleens from treated and control mice. A sample experiment is shown in Fig. 4, top panel. Quantitation confirms the Western blot data that AS c<sub>n</sub> oligonucleotide treatment of mice leads to reduced bcl-2 protein levels in lymphoma cells in the spleen (Fig. 4, bottom panel). This also reveals maximal reduction at the 300-μg dose (P < 0.02 for comparison of 300- and 200-μg doses; no significant difference for comparison of 400- and 300-μg doses).

Therapeutic Efficacy of c<sub>n</sub> AS Oligonucleotides. We then sought to determine the therapeutic efficacy of this immu-
noglobulin-targeted down-regulation of bcl-2 and induction of apoptosis in WSU-FSCCL cells in scid mice. Because cells reappeared in ascites 1 week after an infusion of oligonucleotides at a time when mice had significant tumor burden, we chose to give weekly injections before tumor had visibly developed. Beginning 72 h after cell injection, 200 μg of AS or control oligonucleotides were infused once weekly until mice were dead or euthanized. By 9 weeks, abdominal distension by lymphoma was visible in control, but not cμ-AS-treated, mice (Fig. 5). As seen in Fig. 6, AS oligonucleotides significantly prolonged survival ($P < 0.001$). Median survival was 10.5 ± 0.5 week for untreated mice and 11.0 ± 0.2 week for mice treated with the control oligonucleotide but extended to 16.7 ± 2.4 weeks for the AS-treated animals. At necropsy, the AS-treated mice generally had similar disease distribution as controls. One mouse, however, was sacrificed with hind limb paralysis found, attributable to meningeal infiltration with lymphoma and had minimal systemic tumor burden, whereas a second was apparently cured, surviving >1 year and remaining PCR negative for bcl-2-cμ.

A shorter, more dose-intensive schedule of oligonucleotide administration has generally been used. We tested a three times weekly schedule for six doses beginning 1–3 weeks after cell injection (Fig. 7). Median survival was 18.5 weeks if AS was begun by day 8 after cell injection ($P < 0.0001$ versus control), and two of six mice were disease free. If lymphoma was allowed to grow for 3 weeks, efficacy, although still statistically significant ($P = 0.0035$), was markedly diminished to 12.5 weeks median survival, compared with 10.9 weeks in the mutated control oligonucleotide-treated group. Thus, this schedule was more effective if tumor burden was low.

To confirm that these results did not merely reflect local tumor control in ascites, we tested s.c. administration of oligonucleotides versus the i.p. route. Oligonucleotides were injected three times weekly for six doses beginning 1 week after cells. In this experiment, median survival for untreated mice was 10.5 weeks, whereas for mutated control oligonucleotides, survival was 10.5 weeks for i.p. and 11.0 weeks for s.c. administration. The AS oligonucleotides prolonged survival to 14.0 weeks with either route of delivery in this experiment. Antisense targeted to cμ and to the bcl-2 translational start site are equally effective in vitro, and we confirmed equal efficacy in vivo as well (not shown). Although the cμ AS oligonucleotides have four base differences from the corresponding murine IgM sequence, to ensure that no effect on murine IgM was confounding the results, we synthesized the corresponding murine sequence, and this had no therapeutic, nor toxic, effect on the mice (not shown).

**DISCUSSION**

We have developed a scid mouse model for human t(14;18)-positive follicular lymphoma. The *in vitro* characteristics and immunophenotype of this cell line are largely reproduced *in vivo*. This model resembles the clinical course of low-grade lymphoma in being disseminated to lymph nodes, liver, spleen, and bone marrow, regardless of whether cells are introduced i.p., i.v., or s.c. The median survival of ~10 weeks after injection of 10 million cells is longer than other models of t(14;18)-positive lymphomas (22). This longer time frame is also more

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**Fig. 3** bcl-2 protein levels in spleen by Western analysis for bcl-2 and CD38. WSU-FSCCL cells were injected i.p. and allowed to grow for 5 weeks. AS-cμ oligonucleotides or control oligonucleotides (400 μg) were injected i.p., followed 2 h later by i.p. injections of 500 mg of Z-VAD. Spleens were harvested 8 h after oligonucleotide administration for all lanes.

**Fig. 4** Flow cytometry for bcl-2 protein expression. Experimental plan was as in Fig. 3, except that doses of oligonucleotides were 200, 300, or 400 μg. Spleens were again harvested 8 h after oligonucleotides (6 h after Z-VAD). Single-cell suspensions were stained for CD45 and bcl-2. Top panel, sample flow data in which the solid line is control oligonucleotide treated; the dashed line is AS-cμ oligonucleotide treated. Bottom panel, quantitation of bcl-2+/CD45+ cells in spleens of three mice/condition. For each dose, AS-cμ oligonucleotide reduces bcl-2+ cells ($P < 0.01$ versus mutant oligonucleotide). For dose response of AS-cμ oligonucleotide, $P < 0.012$ for 300 versus 200 μg. Bars, SD.
representative of typical lymphoma biology in humans. Meningeal involvement is uncommon in human low-grade non-Hodgkin’s lymphoma but occurs in other scid leukemia/lymphoma models (23). It also develops in our model, primarily in longer survivors after effective treatment.

Follicular lymphoma is characterized by t(14;18), which leads to dysregulated bcl-2 gene expression and prolonged lymphoma cell survival (24, 25). bcl-2 is, therefore, a reasonable therapeutic target. AS oligonucleotides targeted to the bcl-2 translational start site have been active in down-regulating bcl-2 and inhibiting cell growth in vitro (5–10) and in vivo (11–13). bcl-2 is, however, expressed in a variety of normal cells (10, 16). Although short-term down-regulation of bcl-2 has been well tolerated (14), increased apoptosis in these normal tissues may be toxic. In t(14;18) cells, bcl-2 is expressed from a fusion transcript containing the entire bcl-2 coding region and 3’ immunoglobulin sequences. Our underlying hypothesis is that AS oligonucleotides targeted to the non-oncogenic immunoglobulin sequences could down-regulate bcl-2 without concerns of short- and long-term toxicity. These oligonucleotides would be specif-

Fig. 5 Mice 9 weeks after inoculation with $1 \times 10^7$ WSU-FSCCL cells, treated weekly with 200 µg of oligonucleotides. Right, mutated control; left, Cm-AS.

Fig. 6 Survival of oligonucleotide-treated scid/ FSCCL mice. Mice received injections of $1 \times 10^7$ WSU-FSCCL cells i.p. Oligonucleotides were administered i.p. to 10 mice/group, beginning 3 days later at the 200 µg/dose once weekly until death.

- A = Cm-AS-ODN
- B = mut-ODN
- C = Control

Days

# of Mice Surviving

0 2 4 6 8 10

0 20 40 60 80 100 120 140 160 180 200
ically toxic to t(14;18)-positive cells, at most leading to a transient decrease in immunoglobulin expression by B cells. Such hypogammaglobulinemia would not be expected to be clinically significant.

In WSU-FSCCL cells, the predominant RNA transcript contains bcl-2 fused to J H and then c m. We reported previously that AS oligonucleotides targeted to the C H-2 region of c m effectively down-regulated bcl-2 and induced apoptosis in FSCCL cells in vitro (18). Here we show that these AS oligonucleotides targeted 39 of the bcl-2 coding region prolong the survival of scid-FSCCL mice. Although it may not be surprising that i.p. injection of AS oligonucleotides is able to clear ascites of human cells, we have also demonstrated systemic effects of i.p. injection by measuring effects in the spleen. Further, s.c. oligonucleotide injection gave similar survival results as i.p. injection.

As expected, apoptosis is induced by down-regulation of bcl-2. The time course of apoptosis is more rapid than expected from the previously reported t1/2 of bcl-2 protein (5). This suggests that the bcl-2 half-life may be shorter in these cells, although this has not been formally determined. By blocking the execution of caspase-mediated apoptosis with the caspase inhibitor Z-VAD, we have prevented this rapid cell death and trapped cells in a bcl-2-low but viable state.

Although these AS oligonucleotides are active in vivo, they rarely cure the mice at this dose and schedule. Higher doses, altered schedules of administration, and/or prolonged therapy may be beneficial. The AS oligonucleotides are less effective with higher tumor burden, which suggests that attaining minimal residual disease with chemotherapy might then permit more efficacious use of these oligonucleotides. In addition, because bcl-2 prevents apoptosis, including that induced by chemotherapy, bcl-2 down-regulation has been shown to be chemosensitizing (7, 9, 11, 26). Thus, combining AS oligonucleotides to down-regulate bcl-2 along with chemotherapy is a rational approach we are investigating to enhance AS effects.

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