Enhanced efficacy of therapy of anti-CD20 antibody with Locked Nucleic Acid antisense oligonucleotide targeting Bcl-2 in human Burkitt’s lymphoma xenografts

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Background

Cell survival by obliterating programmed cell death in cancer cells has been closely linked to high Bcl-2 expression. The therapeutic potential of reducing Bcl-2 in cancer cells has been documented and resistance to existing cancer therapies has been linked to Bcl-2.

Materials and Methods

The RNA antagonist, SPC2996, is a 16-mer oligonucleotide incorporating Locked Nucleic Acid (LNA) with unique high affinity binding to Bcl-2 mRNA and enhanced resistance to nucleic digestion. In cell cultures, SPC2996 shows potent, specific and long-lived reduction in Bcl-2 mRNA and protein levels with an IC50 in the low nanomolar range. In vivo studies demonstrated substantial down-regulation of Bcl-2 mRNA was observed in tumors after intravenous administration of SPC2996. SPC2996 has completed a phase I trial in CLL where a dose response effect of SPC2996 was observed with higher doses giving improved effects on lymphocyte counts, lymph nodes, time to progression and overall responses.

RESULTS

Here we report on the anti-tumour activity of SPC2996 alone and in combination with Rituximab in SCID mice bearing disseminated Raji or Namalwa human Burkitt’s lymphoma. The Raji cell line has a high CD20 expression and shows sensitivity to Rituximab while the more aggressive Namalwa cell line has very low CD20 expression and shows resistance to Rituximab. SPC2996 was administered IV daily at 5mg/kg for 14 consecutive days starting on day 1 and IV weekly at suboptimal doses for 3 weeks. All treatments were started at day 4 after tumour cell injection (xenografting). A scrambled oligonucleotide was given as a control.

- In the Raji model the combination of SPC2996 plus Rituximab showed significantly longer survival than either treatment alone and a T/C value of 310.6 compared to Rituximab plus the scrambled control oligonucleotide.

- Analysis of the bone marrow at day 18 after Raji tumour cell injection showed no significant differences in the percentage of human tumor cells from 27.7% in mice treated with the scrambled oligonucleotide to 33.9% with SPC2996 alone and no significant difference above background level with the combination of SPC2996 plus Rituximab.

- In the Namalwa model SPC2996 alone had no significant effect on survival but treatment with SPC2996 alone showed significant prolonged survival with a T/C value of 143.3 compared to Rituximab plus control oligonucleotide. Treatment with the combination of SPC2996 plus Rituximab significantly prolonged the survival even further with a T/C value of 195.5 compared to Rituximab plus oligonucleotide.

- The percentage of human tumor cells in the bone marrow at day 14 after Namalwa tumour cell injection showed a reduction from 14.5% to 2.7% in mice treated with the scrambled control oligonucleotide to a level slightly above the background staining with both SPC2996 alone and in combination with Rituximab while Rituximab alone showed 6.6% human tumor cells in bone marrow.

CONCLUSION

We have here presented data on the LNA containing RNA antagonist SPC2996 targeting Bcl-2 in two different human Burkitt's lymphoma xenograft models. In the disseminated Raji Burkitt’s lymphoma model SPC2996 administered alone displayed a moderate antitumour activity. In contrast SPC2996 showed a marked and highly significant improvement of the antitumour activity when combined with Rituximab. The combination of SPC2996 plus Rituximab showed a marked and highly significant improvement of the antitumour activity compared to SPC2996 alone and Rituximab alone.