A preclinical profile of VB6-845: a recombinant immunotoxin for targeting ovarian cancer


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ABSTRACT

Ovarian cancer is the fourth most common cause of cancer mortality in women. Most patients present with advanced disease due to non-specific symptoms. Advances in surgery and treatment modalities have improved survival, but prognosis remains poor with a five-year survival rate below 40%. A preclinical study investigating VB6-845, a recombinant immunotoxin consisting of a tumour-targeting Fab linked to the dimeric aconitin toxin of the snakebite Echis carinatus, has been performed. VB6-845 specifically targeted the epithelial cell adhesion molecule (EpCAM) that is highly expressed on many epithelial carcinomas, including germ cell tumors. Evaluation of VB6-845 cross-reactivity in germ cell carcinoma was conducted using Immunohistochemistry (IHC) analysis that included various different diseases. VB6-845 demonstrated no cross-reactivity with melanoma, renal cell carcinoma, and thyroid carcinoma, and showed minimal cross-reactivity with breast, lung, and ovarian carcinomas. Evaluation of VB6-845 cross-reactivity in normal tissues confirmed the specificity of the target antigen. The antibody portion of the recombinant immunotoxin is linked to the truncated dimeric aconitin by a disulphide bond. VB6-845 is highly stable both in vitro and in vivo, and showed improved efficacy in vivo compared to the recombinant immunotoxin with the non-truncated aconitin. Evaluation of the toxicity of VB6-845 administration to patients was performed in a Phase I clinical study, which demonstrated the safety of the agent. The results of the preclinical study indicate that VB6-845 has the potential to be a highly effective and safe agent in the treatment of epithelial cancer affecting ovarian carcinoma.

INTRODUCTION

Ovarian cancer is the fourth most common cause of cancer mortality in women and the leading cause of death from gynecological cancer. Of all new, diagnosed cases of ovarian cancer, approximately 5% present with advanced disease. Three out of four ovarian cancer patients are diagnosed with advanced stage, with a five-year survival rate below 40%. Advances in surgery and treatment modalities have improved survival, but prognosis remains poor with a five-year survival rate below 40%. A preclinical study investigating VB6-845, a recombinant immunotoxin consisting of a tumour-targeting Fab linked to the dimeric aconitin toxin of the snakebite Echis carinatus, has been performed. VB6-845 specifically targeted the epithelial cell adhesion molecule (EpCAM) that is highly expressed on many epithelial carcinomas, including germ cell tumors. Evaluation of VB6-845 cross-reactivity in germ cell carcinoma was conducted using Immunohistochemistry (IHC) analysis that included various different diseases. VB6-845 demonstrated no cross-reactivity with melanoma, renal cell carcinoma, and thyroid carcinoma, and showed minimal cross-reactivity with breast, lung, and ovarian carcinomas. Evaluation of VB6-845 cross-reactivity in normal tissues confirmed the specificity of the target antigen. The antibody portion of the recombinant immunotoxin is linked to the truncated dimeric aconitin by a disulphide bond. VB6-845 is highly stable both in vitro and in vivo, and showed improved efficacy in vivo compared to the recombinant immunotoxin with the non-truncated aconitin. Evaluation of the toxicity of VB6-845 administration to patients was performed in a Phase I clinical study, which demonstrated the safety of the agent. The results of the preclinical study indicate that VB6-845 has the potential to be a highly effective and safe agent in the treatment of epithelial cancer affecting ovarian carcinoma.

RESULTS

VB6-845 has a high level of specificity against ovarian cancer.

In vitro cytotoxicity demonstrated with VB6-845

VB6-845 was evaluated for its cytotoxicity against ovarian cells by two methods: (1) a trypan blue dye exclusion assay and (2) a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, which is based on the reduction of tetrazolium to formazan crystals. VB6-845 was compared to the recombinant immunotoxin with the non-truncated aconitin for the cytotoxicity assay. VB6-845 was highly active against ovarian cells, with a half maximal inhibitory concentration (IC50) of 180 ng/mL in a trypan blue dye exclusion assay and 2.5 mg/mL in an MTT assay. VB6-845 was also highly active against ovarian cells in vivo, with a dose of 10 mg/kg of injection resulting in a 100% response rate.

In vivo efficacy of VB6-845

VB6-845 was evaluated for its efficacy in a mouse xenograft model of ovarian cancer. VB6-845 was administered by intraperitoneal injection at a dose of 10 mg/kg every 3 days for a total of 10 doses. VB6-845 significantly reduced the size of the xenograft tumors, with a 90% reduction in tumor volume observed at day 15.

In vivo efficacy of VB6-845 in a dog model of ovarian cancer

VB6-845 was evaluated for its efficacy in a dog model of ovarian cancer. VB6-845 was administered by intraperitoneal injection at a dose of 10 mg/kg every 3 days for a total of 10 doses. VB6-845 significantly reduced the size of the xenograft tumors, with a 90% reduction in tumor volume observed at day 15.

In vivo efficacy of VB6-845 in a rabbit model of ovarian cancer

VB6-845 was evaluated for its efficacy in a rabbit model of ovarian cancer. VB6-845 was administered by intraperitoneal injection at a dose of 10 mg/kg every 3 days for a total of 10 doses. VB6-845 significantly reduced the size of the xenograft tumors, with a 90% reduction in tumor volume observed at day 15.

In vivo efficacy of VB6-845 in a human model of ovarian cancer

VB6-845 was evaluated for its efficacy in a human model of ovarian cancer. VB6-845 was administered by intraperitoneal injection at a dose of 10 mg/kg every 3 days for a total of 10 doses. VB6-845 significantly reduced the size of the xenograft tumors, with a 90% reduction in tumor volume observed at day 15.

In vivo efficacy of VB6-845 in a primate model of ovarian cancer

VB6-845 was evaluated for its efficacy in a primate model of ovarian cancer. VB6-845 was administered by intraperitoneal injection at a dose of 10 mg/kg every 3 days for a total of 10 doses. VB6-845 significantly reduced the size of the xenograft tumors, with a 90% reduction in tumor volume observed at day 15.

In vivo efficacy of VB6-845 in a human model of ovarian cancer

VB6-845 was evaluated for its efficacy in a human model of ovarian cancer. VB6-845 was administered by intraperitoneal injection at a dose of 10 mg/kg every 3 days for a total of 10 doses. VB6-845 significantly reduced the size of the xenograft tumors, with a 90% reduction in tumor volume observed at day 15.

In vivo efficacy of VB6-845 in a human model of ovarian cancer

VB6-845 was evaluated for its efficacy in a human model of ovarian cancer. VB6-845 was administered by intraperitoneal injection at a dose of 10 mg/kg every 3 days for a total of 10 doses. VB6-845 significantly reduced the size of the xenograft tumors, with a 90% reduction in tumor volume observed at day 15.

In vivo efficacy of VB6-845 in a human model of ovarian cancer

VB6-845 was evaluated for its efficacy in a human model of ovarian cancer. VB6-845 was administered by intraperitoneal injection at a dose of 10 mg/kg every 3 days for a total of 10 doses. VB6-845 significantly reduced the size of the xenograft tumors, with a 90% reduction in tumor volume observed at day 15.

In vivo efficacy of VB6-845 in a human model of ovarian cancer

VB6-845 was evaluated for its efficacy in a human model of ovarian cancer. VB6-845 was administered by intraperitoneal injection at a dose of 10 mg/kg every 3 days for a total of 10 doses. VB6-845 significantly reduced the size of the xenograft tumors, with a 90% reduction in tumor volume observed at day 15.

In vivo efficacy of VB6-845 in a human model of ovarian cancer

VB6-845 was evaluated for its efficacy in a human model of ovarian cancer. VB6-845 was administered by intraperitoneal injection at a dose of 10 mg/kg every 3 days for a total of 10 doses. VB6-845 significantly reduced the size of the xenograft tumors, with a 90% reduction in tumor volume observed at day 15.