Study to investigate the anti-cancer potential of CV 247 and its constituents dosed to C57BL mice bearing a syngeneic tumour

Introduction

The proposed mechanism of action for CV247 is immunomodulatory. Normally immunocompromised animals xenografted with human tumours would be used to study chemotherapeutics. However with the supposed immunomodulatiory effect they are unsuitable. It is well recognised that in order to have a predictive effect of potential efficacy in man syngeneic tumours must be used. Therefore the syngeneic transplantable Lewis Lung Carcinoma (LLc) was used in immonocompetent mice. It is a highly metastatic and drug resistant murine non-small cell lung (NSCL) tumour. It was a spontaneous epidermal carcinoma found in the lung of a C57BL/6 mouse and established as a cell line that has been widely used to study tumour growth, metastasis and chemotherapy. Gemcitabine has been demonstrated to be efficacious against LLc grafts, and so was deemed a suitable positive control in this experiment.

Objectives

The objectives of the study were:

• To determine the optimum cell number to be administered to mice in order to produce a suitable LL2/LLc1 model for assessing the effect of immunomodulation.
• To determine the efficacy of CV247 and its component parts at various dose levels in LL2/LLc1 tumour grafts.
• To determine the effectiveness of prophylactic and reactive dosing of CV247.

Methods

LL2/LLc1 cells were injected subcutaneously into female C57BL6/J mice. The anti-tumour activity of CV247 was investigated as follows: one group assessed the use of a prophylactic dosing regimen of CV247 administered at 10mL/kg from the day of tumour inoculation, treatment continued for 21 days.
All other regimens commenced 7 days after tumour inoculation. CV247 was dosed daily at 3mL/kg, 10mL/kg and 20mL/kg for 14 days.
Additional groups looked at components of CV247 and included Sodium Salicylate, Sodium Salicylate + Ascorbic Acid, Sodium Salicylate + Ascorbic Acid + Copper Gluconate, Sodium Salicylate + Ascorbic Acid + Manganese Gluconate, all dosed once daily for 14 days. Gemcitabine administered every 3rd day on 5 occasions commencing 1 week after tumour inoculation, was used as a positive control. All treatments were assessed against a common untreated control over a period of 3 weeks.

Results

Gemcitabine (120mg/kg IP) reduced tumour growth when compared to untreated control, however the efficacy was not deemed significant anti-tumour activity. CV247 did not appear to reduce tumour volume, however a reduction in final tumour weight was observed at all the concentrations used. The combination of sodium salicylate + ascorbic acid + manganese gluconate demonstrated a retardation of tumour growth comparable with that of gemcitabine, though again this was not considered significant anti-tumour activity in accordance with NCI guidelines. Sodium salicylate alone was the least effective with regard to tumour weight reduction

Conclusion

This study has demonstrated potential for CV247 to be an anti-tumour agent and supported the requirement for at least 3 of the components to be present to optimize the effect. The decrease in final tumour weight indicates a mechanism for tumour reduction that is not necessarily related to tumour volume. Speculatively it may be suggested that an immunological process is initiated that results in break down the tumour core, therefore reducing the weight (but not size) of LL2/LLc1 carcinomas. It is interesting to note that Gemcitabine (normally a highly active anti-tumour agent) did not demonstrate significant efficacy in this model.

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