Novel cell penetrating formulation of cytotoxic agents administered intratumorally causes complete regression of large tumors and stimulation of an adaptive immune response in BALB/c syngeneic mice inoculated subcutaneously with murine CT26 colon cancer.

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Summary

The Vaccine Branch at the National Cancer Institute and Intensity Therapeutics are collaborating to examine new drug products consisting of potent cytotoxic agents formulated with compounds that improve intracellular and tissue diffusion. Intensity Therapeutics' drug INT230-6 shows strong tumor regression and long term immune-based protection against murine cancers.

Experiments have shown that the new treatment approach is less toxic and more effective than conventional methods.

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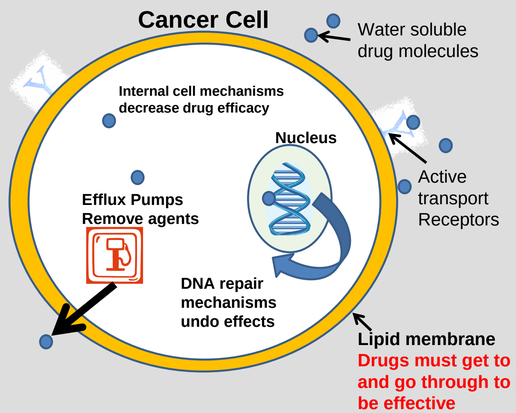
INTRODUCTION

In 2013, the NIH estimated that over 585,000 Americans died of cancer (90% from late stage). Cancer is the second most common cause of death in the US. When surgery is not possible the main treatment option is to use chemotherapy. Yet for late stage or metastatic disease long term patient survival is extremely low and treatment toxicity is high. Here we describe a new immune-based methodology; ***in situ* chemovaccination**. In this approach a novel drug product; INT230-6, (containing 0.5 mg/mL of cisplatin, 0.1 mg/mL of vinblastine formulated with an amphiphilic, cell-penetration excipient; IT-006 at 10 mg/mL) demonstrates a local ablative effect on large murine tumors and stimulation of an adaptive immune response when dosed intratumorally (IT).

FUNDAMENTAL PROBLEMS OF CURRENT CHEMOTHERAPY EFFECTIVENESS

Cytotoxic drugs need to disperse throughout a tumor and enter the cells. Many standard agents enter cells via receptors. Cancer cells are highly resistant to drug diffusion. Often cell death requires high intracellular drug levels.

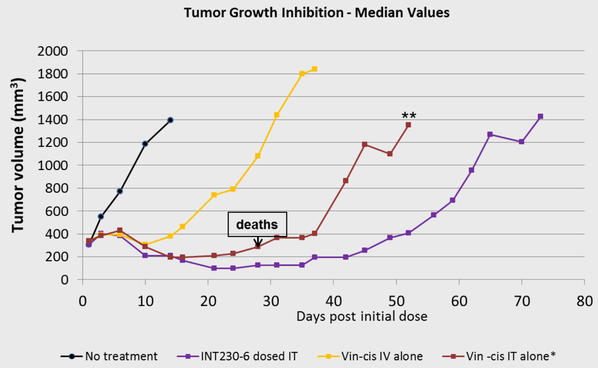


NOVEL TECHNOLOGY

The use of cell penetration enhancer excipients improves drug diffusion and cell permeation allowing for higher intracellular drug concentrations and greater tumor cell death.

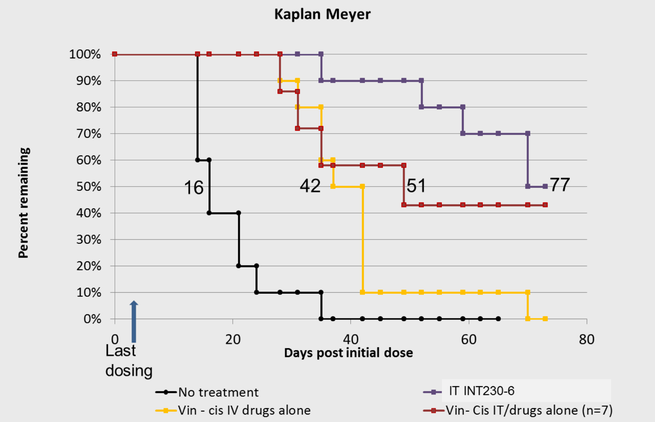
IN VIVO DATA & RESULTS

We conducted a study in syngeneic female BALB/c mice inoculated subcutaneously (SC) with $1x10^6$ CT26 cells. Tumors grew to mean volumes of $325mm^3$ predose. The study comprised four groups: 1) no treatment, 2) INT230-6 given IT, 3) the drugs given intravenously (IV) alone and 4) the drugs given IT without the excipient. Animals in the IT treatment groups received 0.1 mL per $400mm^3$ of tumor volume for 5 days. IT & IV doses were comparable. There was no adjustment for body weight. Tumor growth inhibition was best observed in the group given INT230-6.

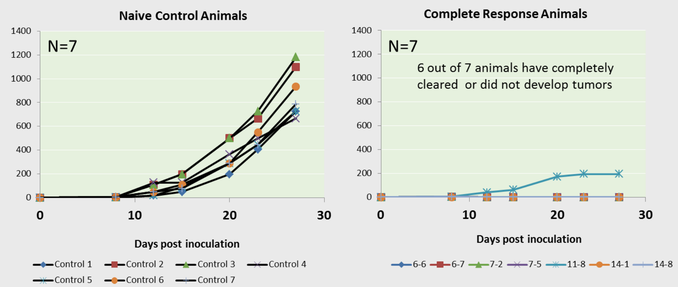


Median overall survival (MOS) for no treatment was 16 days versus 77 days for INT230-6, ratio of 0.2078 with 95% CI of 0.074 to 0.637 with a hazard ratio using Mantel-Haenszel of 0.03501 (95% CI 0.00862 to 0.1422).

The INT230-6 group's MOS survival exceeded that of the IT dosing without the excipient and the IV dosing group (42 days) ($p<0.0002$). Twenty percent of animals had a complete response (CR) using INT230-6 with the single drug cycle.



CR animals along with naïve controls were re-inoculated SC with $1x10^6$ CT26 cells then IV. Nearly ninety percent of the CR animals were fully protected against both SC and IV re-inoculation.



DISCUSSION & CONCLUSIONS

The observed long-term protection against CT26 cancer re-inoculation may be due to an adaptive immune response induced by the dying tumor cells. Thus In situ chemovaccination using INT230-6 may be an improved method to treat late stage and metastatic cancer.