A Phase I, open label, cohort study of two doses of Coxsackievirus A21 given intratumorally in Stage IV melanoma

D.R. Shafren, B.M. Smithers, M.Formby

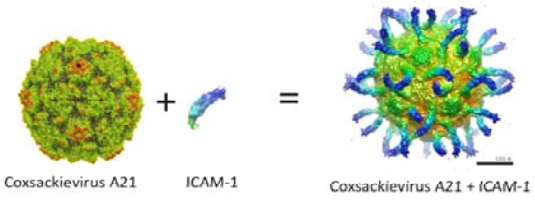
Viralytics Ltd, Pymble, Sydney, New South Wales, Australia ; Department of Medical Oncology, Princess Alexandra Hospital, Queensland, Australia ;
Department of Histopathology, John Hunter Hospital, Newcastle, New South Wales, Australia

Introduction

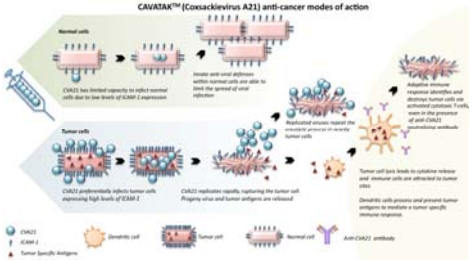
Coxsackievirus A21 (CVA21: CAVATAK™) is a naturally occurring Picornavirus, which induces mild upper respiratory symptoms during natural infection of humans. CVA21 also displays potent oncolytic activity against both *in vitro* cultures of human cancer cells and against *in vivo* xenografts of human cancers in mouse models of melanoma, prostate cancer, breast cancer and multiple myeloma, all which exhibit high surface ICAM-1 expression. In mouse human melanoma xenograft CVA21 challenge models, progeny virus released from infected cells is capable of targeting adjacent cells, entering the systemic circulation, and destroying micro-metastatic foci.

Coxsackievirus A21

- Coxsackievirus A21 (CAVATAK™,CVA21) is a human enterovirus C genus of the family *Picornaviridae*;
- Coxsackievirus A21 is a naturally occurring replication competent virus;
- Causes mild upper respiratory illness "common cold";
- Coxsackievirus A21 binds to the N-terminal domain of intercellular adhesion molecule-1 (ICAM-1);
- Targets cancer cells expressing high surface levels of ICAM-1;
- Numerous different types of cancer cells express high levels of ICAM-1.



Coxsackievirus A21: Mode of action



Objectives

Primary Objective

•To determine the safety of two equal doses of CVA21 given by intratumoural injection 48 hours apart, with total doses given of $2x10^7$ $TCID_{50}$, $2x10^8$ $TCID_{50}$ and $2x10^9$ $TCID_{50}$

Secondary Objectives:

•To evaluate clinical responses (reflecting potential CVA21 activity) of the injected nodules as measured by callipers and ultrasound.
•To determine clinical responses in non-injected tumours, as measured by CT scan.
•To establish predictors and correlates of adverse events.

Methods: Dosing schedule

A single cutaneous melanoma deposit of 9 stage IV melanoma patients (3 cohort of 3 patients) was injected with 2 doses of CVA21 (1.0 $x10^7$ $TCID_{50}$ 1.0 $x10^8$ $TCID_{50}$ or 1.0 $x10^9$ $TCID_{50}$; Viralytics Limited) 48 hours part. The viral inoculum was diluted to 10% of the target lesion in saline up a maximum of 10mL. The average longest diameter of the injected lesions was 3.2 ± 0.9 cm.

Results

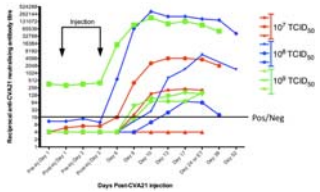


Figure 1. Timecourse of the development of patient serum anti-Coxsackievirus A21 neutralising antibody.

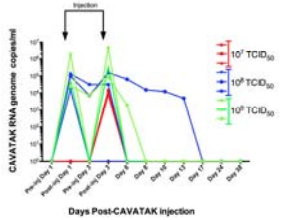


Figure 2. Serum levels of Coxsackievirus viral RNA as monitored by qRT-PCR.

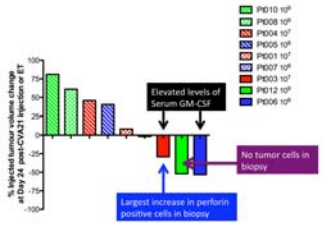


Figure 3. Changes in injected lesion volumes as assessed by ultrasound measurement.

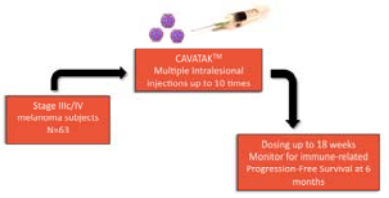
Discussion

- Nine patients tolerated two intralesional injections of CVA21 up to a final accumulated dose of 2 x 10^9 $TCID_{50}$, as such a MTD of CVA21 in excess of 10^9 $TCID_{50}$ was not reached.
- Following CVA21 injections, 5 of 9 (55.6%) patients experienced transient/stable reductions in injected tumor volume or tumor stabilization
- No objective responses were observed, however, 2 patients displayed stable disease as assessed by RECIST 1.0 following CT evaluation.
- CVA21 viral RNA was detected by qPCR in 3 of 5 injected lesions on trial termination, even in the presence of high level serum anti-CVA21 neutralising antibody.
- Elevated levels of serum GM-CSF were observed from 2 patients displaying notable reductions in the volume of injected lesions, suggesting a possible immune-mediated anti-tumor response.
- No evidence of post-injection CVA21 excretion in urine, feces and sputum was observed.

Conclusions

Potential anti-tumor activity and patient tolerability of intralesionally delivered CVA21, provides a solid foundation for Phase II investigations employing a multi-dose administration schedule to study the efficacy and safety of CVA21 in patients with late stage melanoma and other advanced solid cancers.

Phase II: CALM Study design



VIRALYTICS