Oncolytic herpesvirus therapy for mesothelioma:
a phase I/IIa trial of intrapleural HSV1716 (NCT01721018)

Penella J Woll1, Sarah Danson2, John G Edwards2, Patricia Fisher3 & Joe Conner4
1Academic Unit of Clinical Oncology, University of Sheffield, Sheffield, UK
2Departments of 2Thoracic Surgery and 3Clinical Oncology, Sheffield Teaching Hospitals NHS Foundation Trust
3Virttu Biologics, Dept of Neurology, Southern General Hospital, Glasgow, UK

Background
Malignant pleural mesothelioma remains a major clinical challenge, with limited therapeutic options. Multifocal intrapleural disease can cause disabling symptoms of pain and breathlessness, even in the absence of distant metastases, so an intrapleural treatment approach is attractive.

HSV1716 is a mutated herpes simplex virus that exclusively replicates in and lyses the dividing cells of HSV1716. Its safety, mode of action and potential for efficacy have been demonstrated in patients with melanomas, head & neck cancers and gliomas.

Oncolytic HSV1716 has selective replication competence for human cancer cells and fails to replicate in normal cells. The oncolytic destruction of cancer cells by HSV1716 also results in the release of tumour antigens.

Preclinical data in mesothelioma: Evidence of activity of HSV1716 in mesothelioma has been obtained in an animal model (Kucharczuk et al, 1997). SCID mice were inoculated intraperitoneally with human malignant mesothelioma cells on day 0. Two weeks later, they received intraperitoneal injections of HSV1716. The median survival was increased from 47 days in the control group (n = 9) to 95 days in the treatment group (n=10). In a second experiment (figure), a dose response effect was seen for increasing HSV1716 dose, which was statistically significant (p=0.001).

Clinical trial: A phase I/IIa trial to determine the safety and potential for efficacy of HSV1716 given into the pleural cavity of patients with malignant pleural mesothelioma has started. Groups of patients will be treated with three dose schedules of HSV1716.

Study objectives
Primary objectives:
- To determine the safety and tolerability of HSV1716 given intrapleurally in patients with inoperable malignant pleural mesothelioma.

Secondary objective:
- To obtain evidence of HSV1716 replication and lysis of mesothelioma cells through analysis of pleural fluid and serum samples.

Exploratory objective:
- To assess tumour response by CT using modified RECIST criteria.

Study design
The study is an open label, dose escalation, phase I/IIa trial, in a single clinical centre. Patients with inoperable malignant pleural mesothelioma requiring an intrapleural catheter will receive 1 x 10^5/iu of HSV1716 via the catheter in these dose groups:
- Group A (3 patients) - single dose
- Group B1 (3 patients) - two doses, one week apart
- Group B2 (3 patients) - four doses, at weekly intervals

If any dose limiting toxicity (DLT) is seen at any level, that group will be expanded to establish safety before proceeding to the next dose level. If two DLTs are seen, accrual to that dose level will be stopped.
- Group C - 3 further patients will be treated at the maximum tolerated dose level.

Principal eligibility criteria
- Histologically proven malignant pleural mesothelioma.
- Not suitable for potentially curative surgery.
- Patients with pleural effusions or ‘trapped lung’ who:
  - have an indwelling pleural catheter or
  - require the insertion of an indwelling pleural catheter.
- Performance status 0, 1 or 2
- Adequate haematological, renal and liver function.
- Do not require radio- or chemotherapy within 30 days.
- No other uncontrolled cardiac or respiratory disease or acute infection.
- No immunosuppressive disorders.
- No systemic steroids > 5mg prednisolone/day.
- No prior malignancy within 5 years.
- No previous treatment with viral therapy.

Study procedures
Consenting eligible patients will have the following assessments:

Pre-study
- History & examination
- Bloods
- CXR
- ECG
- CT within 4 weeks of starting study treatment

On-study
- Pleural fluid
- Bloods
- Urine
- Mouth swabs
- All to be taken on treatment days and days 3, 5, 8, 15, 22 and 29 after the last virus dose.
- CT scans on days 29 and 57.

Progress to date
- Approval of the protocol and patient information sheet were obtained from the UK Department of Health Gene Therapy Advisory Committee (GTAC).
- Standard operating procedures (SOP) for the safe handling and disposal of the HSV1716 have been agreed by the sponsors and Sheffield Teaching Hospitals NHS Foundation Trust.
- Opened to recruitment in November 2012.
- Part A has been completed with 3 patients receiving a single intrapleural dose of HSV1716.
  - 3 further patients will be treated at the maximum tolerated dose level.
  - Group B1 (2 doses HSV1716) has now started with 1 patient treated to date

Future studies
- If the phase I/IIa study demonstrates that HSV1716 is taken up by mesothelioma cells in vivo, leading to viral replication and tumour cell lysis, and no unexpected safety issues arise, we plan to develop a phase II protocol testing the efficacy of HSV1716 as an intrapleural instillation in mesothelioma patients.

Summary
A novel phase I/IIa study of oncolytic virus therapy for malignant pleural mesothelioma opened in Sheffield in November 2012. Patients with intrapleural catheters will receive up to 4 doses of HSV1716 through the catheter. The activity of the virus will be assessed by detecting evidence viral replication in the pleural fluid. Detailed safety analyses will be undertaken. If successful, a phase II study of intrapleural instillation of HSV1716 is planned.

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