Gene therapy trials: a patient pathway


Summary
This article describes ongoing gene therapy trials at University Hospital Birmingham NHS Trust for liver, head and neck and prostate cancer treatment. The authors suggest that this research programme might become an alternative option for patients who have not responded to conventional treatments.

Gene therapy trials

Gene transfer
Gene transfer is the process of insertion of one or more genes into the cell. Genes are transferred to cells via vectors. A vector can be physical as in direct naked DNA injection, chemical such as liposomal encapsulation or viral (Morgan and Anderson 1993). Viruses are used as vectors because of their innate ability to insert genetic material into the cytoplasm or the genome of a host cell, that is, they infect. The viral vectors that are used for gene therapy trials are adenoviruses.

Adenoviruses
Adenoviruses were discovered in 1953 as scientists attempted to identify the causative agents of the common cold. In general the viruses currently used in gene therapy are replication deficient, that is, specific regions of the viral DNA essential for replication are deleted.

Current research
At University Hospital Birmingham NHS Trust (UHBT) three virus-directed enzyme prodrug therapy (VDEPT) trials are ongoing for liver, head and neck and prostate cancer treatment. In VDEPT the gene delivered to the cancer cells encodes an enzyme that is able to convert a relatively non-toxic prodrug into a highly cytotoxic compound. The ultimate aim of this therapy is to kill the cancer cells while keeping the systemic concentration of toxic compound at a minimal level (Figure 1).

All the UHBT clinical trials use direct intratumoral injection of a replication deficient adenovirus (CTL 102), encoding the bacterial enzyme nitroreductase (MRL Laboratories 2000a and b). The prodrug CB 1954 is a weak alkylating agent, but when activated by nitroreductase becomes a highly potent bi-functional DNA alkylating agent, that is, a highly cytotoxic compound. CB 1954 is not cell cycle specific once activated unlike most conventional chemotherapies. This approach is augmented by the so-called ‘bystander effect’ in which neighbouring untransduced tumour cells are killed during the prodrug therapy.

Study design
The UHBT trials are divided into two ‘arms’: operable and inoperable (Figure 2). An ‘operable’ patient is one whose tumour is scheduled for surgery. These patients are dosed with adenovirus CTL 102. Cohorts of three patients are given an escalating virus dose. Once evidence of nitroreductase expression is seen at a particular dose of CTL 102, patients with inoperable disease will be treated. These patients will receive adenovirus CTL 102, followed two days later by a fixed systemic dose of CB 1954.

The primary objective of the trials is to assess the safety and tolerability of direct intratumoural administration of an adenovirus. Secondary objectives are to show gene expression of nitroreductase in resected specimens and to observe for evidence of prodrug activation after CB 1954 has been administered to patients who have not responded to conventional treatment.

Patient recruitment
Recruitment to the trials begins when patients attend the relevant clinics. Discussion between nurses and consultants identifies suitable patients. Patients must meet strict inclusion and exclusion criteria set out in the clinical trial protocol: for example they must be over 18 and able to give consent, their condition must be operable and liver, bone marrow and kidney function clinically acceptable. If suitable and interested, patients are given more in-depth explanations about the trial by gene therapy nurses. Information sheets are provided telling patients who have not responded to conventional treatments.
patients what to expect when they participate in the trial.

**Patient screening** Baseline patient screening is performed before gene therapy starts. A clinical oncologist performs a medical examination, obtains a full history and written consent for entry into the trial. The target lesion is routinely screened and measured using ultrasound (for liver tumours). A number of blood investigations are made and the patient has an electrocardiogram and chest X-ray. Patients are tested for active adenovirus infection and if found to have active infection are automatically excluded from the trial. Patients are expected to use contraceptive barrier methods before and at least three months after participation in the trial. If the patient meets all inclusion criteria and investigation results show no evidence of adenovirus infection, he or she is entered into the trial and given an admission date two to five days before the start of therapy.

**Box 1. Overview of main procedures for patients entering the trial**

- Patient identified
- Pre-screening and written consent
- Patient registration into trial
- Relevant department notification
- Isolation room preparation
- Patient admission ward
- Patient isolation
- Virus injection
- Patient discharge from isolation (with negative virus shedding)
- Decontamination of isolation room and removal of waste
- Elective surgery (two to five days post-virus insertion)
- Follow-up care

**Figure 1. Viral delivery of enzymes for prodrug therapy with bystander effect**

**Figure 2. Schematic diagram of gene therapy trial design**

Operable patients

- Virus dose escalation until nitroreductase enzyme expression

Inoperable patients

- Virus dose escalation with fixed dose CB1954 until MTD

Operable patients

- Virus dose escalation until MTD

MTD = maximum tolerated dose
scheduled surgery (Box 1).

**Pre-injection** Unlike conventional drug therapy there are no clear safety guidelines for the use of genetically modified organisms in this clinical trial. To date the infectious spread of viruses has not been observed and the risk to staff appears to be minimal (Tursz et al 1996). It is currently not clear whether safety precautions, such as wearing masks, gloves and gowns should be taken. No known risks have been identified, but general consultation between nursing, medical, biological safety officers and hospital health and safety officers favours universal precautions, such as plastic aprons, gloves and standard hand washing procedures, which are known to be effective in preventing the transmission of pathogens such as hepatitis virus or human immunodeficiency virus. Once it can be shown that transmission of the adenovirus remains only a theoretical risk, the strict isolation procedures can be relaxed.

The pathway described is for operable patients without prodrug administration. On the morning of the adenovirus injection the patient is admitted to an isolation room with ensuite facilities. Personal belongings are discouraged to minimise infection risk. The virus is prepared in a designated pharmacy clean room, by a pharmacist and technician. The patient receives a local anaesthetic, a research nurse and doctor check the virus, and it is then injected directly into the tumour. There is a theoretical risk of virus leakage resulting in a degree of systemic exposure (virus shedding). However, this represents a small but acceptable level of risk as the immune system of the majority of cancer patients will already have encountered a ‘wild type’ adenovirus.

**Post-injection** After injection of the virus into the tumour, the patient is required to rest in bed for at least two hours. The research nurses provide a vital role in monitoring the patient and assessing patient tolerance to any side effects of the therapy. Patients might experience flu-like symptoms, tenderness and slight bleeding at the needle injection site. Routine observations are all taken at specified intervals during the day. A risk assessment carried out within the trust states that anyone having direct patient contact must wear disposable protective clothing that must be discarded as clinical waste before leaving the isolation room. The Health and Safety Executive Contained Use Regulations (HSE 2000) cover the disposal of genetically modified organisms. Clinical waste disposal is dependent on whether waste has been in direct contact with

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### Table 1. Outpatient follow up

<table>
<thead>
<tr>
<th>Days after virus injection</th>
<th>Months after virus injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>-14 (Pre-screening)</td>
<td>0, 1, 7, 14, 21</td>
</tr>
<tr>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Blood samples (haematology, clotting, biochemistry, tumour markers)</td>
<td>– (also virology and blood group)</td>
</tr>
<tr>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Throat swab, stool sample and urine sample for anti adenovirus antibodies</td>
<td>–</td>
</tr>
<tr>
<td>Blood samples for anti adenovirus antibodies</td>
<td>–</td>
</tr>
<tr>
<td>Routine blood pressure, pulse, temperature and weight</td>
<td>–</td>
</tr>
<tr>
<td>Review by doctor and research nurse</td>
<td>and patient written consent</td>
</tr>
<tr>
<td>Electrocardiogram, chest X-ray and ultrasound (if applicable)</td>
<td>–</td>
</tr>
<tr>
<td>Discharge if viral shedding clear</td>
<td>–</td>
</tr>
</tbody>
</table>

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**Note:**

- Table 1 outlines the outpatient follow up protocol for patients undergoing adenovirus treatment. The table details the scheduled visits and tests to monitor patient recovery and ensure patient safety.
- The "Pre-screening" period covers days -14 to 0, followed by monthly visits up to 12 months post-injection.
- Tests include blood samples for various biomarkers, throat swabs, stool and urine samples, routine vital signs, medical reviews, and diagnostic tests like electrocardiograms and chest X-rays.
- Discharge criteria are based on viral shedding status, with clear shedding requiring further isolation.

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**References:**

- Tursz et al 1996
- Health and Safety Executive Contained Use Regulations (HSE 2000)
Box 2. Nurse involvement in the gene therapy trial

- Education of staff likely to be involved directly or indirectly about risks and procedures, as well as underlying theory on treatment being used.
- Writing and implementation of standard operating procedures.
- The process for recruitment of patients for the trial generally follows the path of attending the liver, head and neck and prostate clinics.
- Assessing suitability according to the clinical protocol for any patient entering the gene therapy trial, which has inclusion and exclusion criteria that must be met.
- Arranging outpatient appointment for patients to attend oncology clinic if they give verbal consent to enter into the trial.
- Patient information and informed consent, co-ordination of care for patients during trial and making sure that patients’ GPs have been notified.
- Arranging all patients’ required pre-screening investigations as stipulated in the protocol, that is, ultrasound, electrocardiogram, chest X-ray, blood tests, plasma for anti-adenovirus antibodies, nasal, anal, throat swabs and urine specimen for adenovirus.
- Educating and informing patients of what to expect during their participation in the trial and what investigations will be carried out at those given times.
- Psychological care which is unique partly due to the limitations of isolation, disease and boredom.
- Checking bed availability on the oncology ward and maintaining links with the ward nurses. Identifying what room to use and equipment to be used.
- Notifying relevant departments of patients’ impending admission, that is, pharmacy (dispensing virus), laboratories (blood samples), mortuary (waste disposal), microbiology (waste disposal), domestic (cleaning of floor with protective coat which may have been removed during cleaning), portering services (taking sample to laboratories), liver high dependency unit, liver, maxillofacial and urology surgeons, relevant theatres, histopathology, health and safety officer and decontamination officer (decontamination of surgical instruments).
- Assisting the doctor during the intratumoural injection of the adenovirus.
- Management of potential side effects immediately after the insertion of the adenovirus.
- Ensuring that patients are not discharged from the isolation room until they have been cleared of virus shedding.
- Continuation of care during treatment and subsequent follow-up visits for a year.

REFERENCES
Rhodes Professor D Kerr Professor D Kerr Professor of Cancer Research Network, University of Oxford.
The Institute for Cancer Studies Dr Dan Palmer Research Fellow.
Dr Nick James Senior Lecturer in Clinical Oncology.
John Ellis Development Project Manager at ML Laboratories.
Special thanks to the liver and maxillofacial surgeons and all the gene therapy team who are involved in the planning and execution of the ongoing trials.

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The role of the gene therapy nurse

It is the role of gene therapy research nurses to educate members of the nursing team and the wider multidisciplinary team directly or indirectly involved in patient care about gene therapy. Gene therapy nurses have an important role in the multidisciplinary team, reinforcing explanations and information about gene therapy, the treatment, associated side effects, long-term monitoring and patient care plans. It is vital that nurses educate and collaborate with other healthcare professionals because they are instrumental in co-ordinating the patient’s overall care. Box 2 details nurse involvement in the trial.

Conclusion

The primary objective of the trial is to determine the safety and tolerability of intratumoural delivery of adenovirus CTL 102 and the secondary objective is to assess the effectiveness of prodigal activation after CB 1954 has been administered. Once a virus dose that expresses a significant level of nitroreductase enzyme is reached, recruitment will expand to incorporate patients with inoperable cancer. A research programme like this might become another option for patients who have not responded to conventional treatments. Gene therapy is an innovative and exciting concept in the field of clinical research, although it will take time and large numbers of patients to demonstrate efficacy.

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