Adverse effects of gene therapy

Gene therapy can cause leukaemia: no shock, mild horror but a probe

ME Gore

Gene Therapy (2003) **10,** 4–4. doi:10.1038/sj.gt.3301946

The recent news that a child participating in a flagship gene therapy trial had developed cancer, almost certainly as a result of the treatment strategy, rocked the gene therapy community. However, should similar trials be halted indefinitely, possibly at the expense of other very sick children?

There are over 600 clinical trials of gene therapy completed, ongoing or pending throughout the world. Almost 2000 patients have been entered into these trials and about 40 have been children with disorders attributable to mutations in single genes (monogenic). Such diseases are rare but are the best candidates for treatment with gene therapy.

X-linked severe combined immunodeficiency (X-linked SCID) is one such disease that is devastating. Those affected die young, often within the first year of life. Bone marrow transplantation from a matched donor is an effective treatment, but matched unrelated donors are rare. Moreover, transplantation of mismatched bone marrow has a high mortality rate (20–30%), and even when successful can result in long-term complications. One of these complications is the possibility of treatment-induced cancer.[1]

It was attempts to find an alternative treatment for X-linked SCID that resulted in one of the first great success stories for gene therapy. In their landmark clinical trial, Alain Fischer's group successfully treated children with X-linked SCID with genes delivered using retroviral vectors.[2]

Two and a half years after treatment, one of the patients involved in the Fischer trial has developed a peripheral T-cell count that is 10 times normal. In addition, the patient's T cells appear to be monoclonal and over-expressing a potential oncogene found at the site of retroviral insertion.[3,4] This site has been identified as being the first intron of the LMO-2 gene on chromosome 11.[3,4] LMO-2 is involved in the development of both the lymphoid and myeloid series and is the site of a translocation that occurs in leukaemia.

These observations clearly suggest that retroviral gene insertion may have been the cause of the leukaemia here. However, other factors such as genetic background and preceding viral infection may have also played a role in the development of this child's disease. A press release from the French regulatory authority rather coyly describes this child's condition as a 'lymphoproliferative disorder': perhaps acute T-cell leukaemia might be another description of this complication.[3]

Long-term integration of gene sequences into a patient's genome is the very property that makes retroviruses attractive vectors for delivering genes to correct inherited monogenic disorders. Only a few studies in animal models of gene therapy have suggested that vector-mediated insertional mutagenesis could be a problem. However, its spectre has always loomed over the field and now it has apparently been made flesh.

In France, the trial sponsor and the Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSPS) have put a hold on this trial. Similarly, the Biologicals Respone Modifiers Advisory Committee of the FDA's Center for Biologics Evaluation and Research (CBER) halted the recruitment of patients for three similar US studies. Both agencies commented that these actions are 'as a precautionary measure, and until analysis and identification of the mechanism(s) responsible' and 'pending further analysis of this event'.[3,4]

In experimental medicine, serious side effects have to be considered in relation to their predictability, their frequency and their severity. In UK trials of gene therapy for inherited disorders that have involved retro viral vectors, patients and relatives have always been specifically warned of the danger of insertional mutagenesis leading to cancer. Similarly, the Fischer trial considered this to be a possibility and warned the families of the patients who were participating.

It is very unusual for a serious adverse event (SAE) that patients have been formally informed about to halt patient recruitment for phase I or II studies. The frequency of a side effect is impossible to assess in the early stages of any trial, and if a predicted SAE occurs, it is more usual to institute extra reporting and monitoring mechanisms than to stop a study.

In this case, the SAE developed $2\frac{1}{2}$ years after treatment. Thus, if one wished to suspend patient recruitment in order to assess this event more fully, the only logical course of action would be to stop patient entry for at least this length of time. Even this would not be an entirely accurate assessment of the situation, because we know from longitudinal studies in cancer patients and retrospective analyses of bone marrow recipients, that the risk of subsequent malignancy is very hard to predict until many years have passed.

Long-term follow-up clinical data is always going to be a vital component of any risk assessment of this (or any other) gene therapy strategy. It is thus illogical to put such trials 'on hold'. It would be more consistent to close them; after all suspending patient recruitment for the required time to complete accurate risk assessment (3–5 years) is tantamount to closure. Further laboratory work alone will not give us an answer to the frequency of treatment-induced malignancy in patients treated with retrovirally based gene therapies.

In the UK, the Department of Health's Gene Therapy Advisory Committee (GTAC) suggests that clinical work should continue albeit with renewed caution. New clinical and laboratory information will be assessed prior to any children being recruited in the future. Permission for treatment will be sought on a case-by-case basis.[5] Thus, independent risk assessment can be made for each individual in the light of the very latest data.

Keeping the trial open in this way allows a balance to be struck between risk and caution. Perhaps the most important feature of this compromise position is that parents are drawn in closer to decisions that affect the conduct of clinical trials that have a direct relevance to their children's desperate plight. Interestingly, it is reported that advice to the FDA has now changed and it is now more in line with the GTAC's view, which is that these studies should conti-nue to proceed, but with extra caution.

The toxicity of any treatment needs to be evaluated in two contexts: what is the therapeutic intent (palliative or curative) and what are the other available treatment options? The intent of gene therapy is curative and the alternative of a bone marrow transplant anyway carries with it the risk of inducing a malignancy. Furthermore, the options for children with X-linked SCID if they do not have a matched sibling are pretty dismal.

Parents have always known that there is a risk of treatment-induced malignancy from retrovirally based gene therapies. This recent sad news does not give them any fundamentally new information; clinicians involved in these trials will still warn of the risk of malignancy and this warning will remain in patient information sheets. I suspect shutting down clinical trials in this area is not what the parents of these children want. ■

ME Gore is in the Department of Medicine, Royal Marsden Hospital, London, UK.

e-mail: martin.gore@rmh.nthames.nhs.uk

1 Leiper AD. Non-endocrine late complications of bone marrow transplantation in childhood: Part II. *Br J Haematol* 2002; **118**: 23–43.
2 Cavazzana-Calvo M *et al*. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. *Science* 2000; **288**: 669–72.
3 Communique de Presse, Déficit Immunitaire Combiné Sévère: suspension d'un essai clinque. *Agence Francaise De Securite Sanitaire Des Produits de Sante*, 3 October 2002.
4 Food and Drug Administration Center for Biologics Evaluation and Research, Biological Response Modifers Advisory Committee, Meeting # 33, October 10th, 2002.
5 Press Release, Gene Therapy Advisory Committee Issues Advice on X-SCID Gene Therapy Trials. *Department of Health*, 3 October 2002.