

# Reflections on the importance of strict adherence to treatment protocols: acute lymphoblastic leukaemia in children in the 1970s in the US and the UK

**Julian Peto**

NCDEU, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

**Corresponding author:** Julian Peto. Email: julian.peto@lshtm.ac.uk

Collaboration among paediatric oncologists in developing treatment for leukaemia in childhood is one of medicine's most remarkable successes.<sup>1</sup> In 1974, when I joined Richard Doll's Cancer Epidemiology Unit in Oxford, I took over from Peter Smith as the statistician responsible for analysing the Medical Research Council trials of treatment for acute lymphoblastic leukaemia in children. At that time, it was difficult to compare the results of trials done in different countries: the various research groups used different definitions of initial remission; patients who had not achieved remission were sometimes excluded; 'high-risk' patients (variously defined by white blood count and age) were treated differently, or actually excluded in some studies; and many trials were small and not randomised. Moreover, results were rarely published until several years after a trial had begun. As a result of this situation, the Medical Research Council Childhood ALL Working Party had to depend on UK data as a guide to treatment and the design of additional trials.

There were, however, some features in common. Treatment protocols developed in the USA had been used in most Medical Research Council trials since 1970. Standard elements included induction chemotherapy, central nervous system radiotherapy and prolonged maintenance chemotherapy. This combination had produced much longer disease-free survival than the treatment protocols used in the 1960s, but it was not clear how to achieve further improvement. The alternatives tried in the 1970s involved experimentation with little theoretical or evidential justification, such as intermittent rather than continuous chemotherapy, or adding cyclophosphamide, which also resulted in interruption of standard chemotherapy.

During a sabbatical spent with Malcolm Pike at the University of California at Los Angeles from

September 1978 to February 1979, I spent a good deal of time with the office of the US Children's Cancer Study Group (USCCSG), which was conducting collaborative treatment trials in childhood acute lymphoblastic leukaemia similar to the Medical Research Council trials. When we used individual patient data to compare the results of UK and US trials using similar treatment protocols, it became immediately clear that the UK results were substantially worse.

I reported this finding to the Medical Research Council Childhood Acute Lymphoblastic Leukaemia Working Party as soon as I returned to the UK. The initial reaction was almost uniformly sceptical, but Tim McElwain (a senior oncologist at the Royal Marsden who subsequently chaired the Working Party) supported me, and I was asked to provide a detailed comparative analysis for the next meeting of the Working Party. The evidence was too strong to be dismissed, and it was agreed that the protocols then being used in the UKALL VI and UKALL VII trials should be replaced by a current USCCSG protocol (CCSG 162). As a result, all patients were treated on this protocol in the UKALL VIII trial, which began in 1980.

The UKALL VIII trial showed a 15–20% improvement in four-year disease-free survival compared with standard treatment used in previous Medical Research Council trials, and a much larger improvement compared with the various alternatives that had been tried since 1972.<sup>2</sup> This was surprising, as induction chemotherapy, central nervous system radiotherapy and maintenance chemotherapy were elements common to the USCCSG 162 trial and the standard Medical Research Council protocols. The only major difference appeared to be the US policy of adhering rigorously to the treatment protocol despite its suppression of white cell production. The

consequent increased risk of pneumonia and other serious infections was reduced by routine use of prophylactic antibiotics. By contrast, the UK policy had been to limit the infection risks by reducing or interrupting treatment with chemotherapy.

With the benefit of hindsight, it seems obvious that the dramatic increase in disease-free survival that had been achieved when long-term maintenance chemotherapy had first been used was likely to be further improved by giving the same chemotherapeutic drugs at higher doses. More intensive early treatment in the subsequent UKALL X trial achieved even better results.<sup>3</sup>

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