The success of paediatric oncological research

The current health service climate has focussed attention on the lack of a solid evidence base for much accepted practice in medicine. Paediatric oncology is more fortunate than most specialties in being able to draw on an evidence base for much of its practice. The speciality has benefitted from a history of robust randomized trials, which also serve as the basis for future improvements.

Paediatric oncology was only recognized in the UK as a speciality in 1977 and hence is an infant compared with the traditional disciplines. Much of the infrastructure is also young, and was established at a time when the importance of evidence-based medicine was only just beginning to be recognized.

Childhood cancer is rare, with only about 1300 new patients aged 0–15 years diagnosed annually in the UK. The resource needed to run both a tumour registry and a clinical trial coordination service for such a patient load is far less than for adult cancer.

The progress made since 1977 has been impressive. In 1977 only 43% of children were treated in specialist centres, now at least 85% are. The UK has 21 centres, and Eire has one, and the activity is coordinated by the United Kingdom Childhood Cancer Study Group (UKCCSG). The provision of data managers in each centre and the full time epidemiological input of the Childhood Cancer Research Group in Oxford allows a comprehensive national tumour registry to be maintained. Thus the building blocks are in place for the UKCCSG to run collaborative multicentre trials, to study the epidemiology of childhood cancer, and to address fundamental questions about the biology of these diseases.

BRICKS IN THE WALL: RANDOMIZED CONTROL TRIALS

Randomized control trials (RCTs) are the holy grail of evidence-based medicine. In paediatric oncology participation in such trials has resulted in a clear improvement in survival over those children not treated in trials. Five-year overall survival for children with acute lymphoblastic leukaemia (ALL) treated between 1990–1994 was 84% for those on trial, while it was only 68% for those not treated on trial (Stiller and Eatcock, 1999), a difference attributed to the increase in standardization of care.

The ethos for RCTs in paediatric oncology has been constantly evolving treatment protocols; the best arm of the previous trial becomes the standard arm of the next one, and a further question(s) forms the subject of the randomization in the new trial. Such an approach does involve designing a new trial before the previous one has ended, and before the results are known. On occasion this means that randomizations have to be carried on into new trials, until the data become available, but long periods with no treatment protocol are avoided.

The first RCTs in paediatric oncology in the UK were the early MRC leukaemia trials in the 1970s (UKALL I–VII) which attempted to apply the 'total therapy' pioneered at St Jude in the late 1960s to children in the UK. The evolution of the treatment of childhood ALL from 1980 to the present day illustrates well the principles described above. UKALL VIII (1980–1984) was the first trial to achieve survival rates comparable to those in the USA, achieving a 5-year disease-free survival of 55% (Eden et al, 1991).

UKALL X (1985–1990) took the basic schedule from UKALL VIII and asked whether the addition of intensive blocks of treatment would improve survival. The 5-year disease-free survival was 71% for patients receiving two intensification blocks and 57% for those receiving none (Chessells et al, 1995).

UKALL XI asked whether further intensification would improve survival, and this randomization was continued into the current trial, ALL97, before demonstrating an 8% increase in survival for those patients receiving a third block (Hann et al, 2000). This success of this strategy is manifest; pre-1980 the 5-year disease-free survival was only 39%, but by the end of the 1990s 5-year disease-free survival was 63%, and overall survival over 80%.

International collaboration of trialists, analysis using standardization of patient stratification, and the comparison of results with specific treatment approaches is facilitating further increases in survival. This success in childhood ALL has been replicated in a wide range of other malignancies; overall survival from all childhood tumours was 50% for children diagnosed between 1977 and 1983, but 75% for children diagnosed between 1994 and 1998. The rarity of many of these tumours has meant that international trials have been needed to recruit sufficient patients to provide timely answers to treatment questions; of 30 UKCCSG trials open at present 18 are international. Increasing international collaboration represents the only realistic way of continuing to improve the outcome for many of these tumours.

EPIDEMIOLOGY: CLUES TO AETIOLOGY

RCTs represent a success story for clinical research in paediatric oncology but a well-validated and verified tumour registry with high ascertainment also allows epidemiological studies, with the aim of elucidating some of the factors involved in the aetiology of childhood cancer.

It has long been suspected that at least some childhood leukaemias might arise as an abnormal response to infection. Evidence has accumulated from incidence changes, space/time clustering, seasonal variation and

population mixing. For common ALL a paucity of infectious exposure in infancy and late or delayed exposure shortly before the onset of symptoms are thought to be important (Greaves and Alexander, 1993).

Backtracking of leukaemia to birth in infant and common ALL, plus studies on twins and triplets, has confirmed a 'multihit' model for leukaemogenesis, involving the initiation of a potentially malignant clone (e.g. the creation of TEL-AML1 fusion genes in ALL), a second genetic event in that clone (e.g. a non-involved TEL gene deletion), and a proliferative stimulus. The latter may involve a genetically determined abnormal response to infection (Wiemels et al, 1999).

A national case control study (1991–1996), now being analysed, addressed the possible carciniogenic role of exposure, in utero or in childhood, to ionizing radiation, hazardous chemicals, and low frequency electromagnetic fields (EMF). The effects of parental germ cell exposure to radiation and chemicals were also investigated. The study included 3838 childhood cancer families and 7629 control families. To date EMF and proximity to high voltage power cables have been exonerated in the UK. Gene–environment interactions are now being extensively investigated to attempt to explain childhood cancer aetiology.

BIOLOGY: UNDERSTANDING MECHANISMS

The early onset of many childhood cancers has lead to considerable advances in the understanding of the heritable components of the transformation from a normal to a malignant cell. The highly influential two-hit hypothesis was originally formulated by Knudson as an attempt to explain bilateral tumours in patients with familial retinoblastoma.

Perhaps even more important in the context of a molecular understanding of tumourigenesis was the discovery of the retinoblastoma gene (Rb) and its mutation in familial retinoblastoma, and the insight that this has provided into the role of tumour suppressor genes in the aetiology of cancer (Marshall, 1991). Perhaps the classic example of a familial cancer syndrome produced by the inheritance of a tumour suppressor gene mutation is the Li–Fraumeni syndrome. In this condition an inherited germ line mutation in the tumour suppressor gene p53 predisposes to soft tissue sarcoma, osteosarcoma, brain tumours and leukaemia.

A further example of the success of basic science research in paediatric oncology is provided by the identification of the usefulness of retinoic acid in the treatment of neuroblastoma. Retinoids are derived from vitamin A and because of the presence of two distinct but interacting receptors (RARs and RXRs) they possess complex biological functions.

In neuroblastoma cells cis-retinoic acid produces apoptosis. A phase I study of 13-cis-retinoic acid showed promise and lead to a large scale randomized Children's Cancer Group trial. This trial showed an event-free survival at 3 years of 46% for those receiving 13-cis-retinoic acid but only 29% for those not. Patients receiving bone marrow transplantation and 13-cis-retinoic acid had a 3-year event-free survival approaching 60% while for those who received neither survival was only 20% (Matthay et al, 1999).

CONCLUSIONS

Research in paediatric oncology has had some considerable success in the last 30 years. Not only have fundamental insights into the mechanisms of tumourigenesis been provided, but testable hypotheses as to the causes of cancer have been generated. The existing framework for the provision of treatment within the context of national and international clinical trials has resulted in spectacular increases in survival, but difficult challenges remain. Survival for patients with some brain tumours, neuroblastoma, osteosarcoma and rhabdomyosarcoma remains disappointing.

Increasing international collaboration in clinical trials, and the introduction of advances in biological understanding of disease into clinical practice offer the means for improval. The foundations are in place, now we must finish what has been started. **HM**

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Chessells JM, Bailey C, Richards SM (1995) Intensification of treatment and survival in all children with lymphoblastic leukaemia: results of UK Medical Research Council trial UKALL X. *Lancet* **345:** 143–8

Eden OB, Lilleyman JS, Richards SM, Shaw MP, Peto J (1991) Results of Medical Research Council childhood leukaemia trial UKALL VIII. *Br J Haematol* **78:** 187–96

Greaves MF, Alexander FE (1993) An infectious aetiology for common acute lymphoblastic leukaemia in childhood? *Leukaemia* **7:** 349–60

Hann I, Vora A, Richards SM et al (2000) Benefit of intensified treatment for all children with acute lymphoblastic leukaemia: results from MRC UKALL XI and MRC ALL97 randomised trials. *Leukaemia* **14:** 356–63

Marshall CJ (1991) Tumor suppressor genes. *Cell* **64:** 313–26

Matthay KK, Villablanca JG, Seeger RC et al (1999) Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. *N Engl J Med* **341:** 1165–73

Stiller CA, Eatcock EM (1999) Patterns of care and survival for children with acute lymphoblastic leukaemia diagnosed between 1980 and 1994. *Arch Dis Child* **81:** 202–8

Wiemels JL, Cazzaniga G, Daniott M et al (1999) Prenatal origin of acute lymphoblastic leukaemia in children. *Lancet* **354**: 1499–503

KEY POINTS

- Paediatric oncology has a strong evidence base and the infrastructure is in place for ongoing randomized control trials to improve treatment.
- Increasing international collaboration in these trials is the way forward.
- Historically, increasing the number of patients treated on trials has produced improvements in outcome.
- Epidemiology continues to address important questions about cancer aetiology.
- Considerable advances have been made in our understanding of basic science; the results of this are starting to be seen in clinical practice.