REVIEW

Clinical trials in paediatric haematology-oncology: are future successes threatened by the EU directive on the conduct of clinical trials?

Chris Mitchell

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It is 100 years since Robert Grieve Hutchison first described the entity that we now recognise as neuroblastoma with bony metastases. Since then, we have moved from a situation where virtually all children with malignancy died to one where more than three-quarters of patients will be long-term survivors. Nevertheless, of the 1400 children with cancer seen in the UK each year, on average around 350 will die, each death untimely and tragic. Much of the early improvement in outcome was due to developments in anaesthesia and surgery, the advent of effective supportive care, and the discovery of effective drugs, such as the folic acid antagonists and adrenocorticoids for the treatment of acute lymphoblastic leukaemia (ALL).[1] The development of multiagent regimens led to further improvements and saw the advent of large multicentre cooperative treatment groups such as the UK Children's Cancer Study Group (UKCCSG), the US Children's Cancer Group (CCG) and the International Society of Paediatric Oncology (SIOP), which made use of formally structured clinical trials. The randomised clinical trial has thus been the mainstay of paediatric oncological practice for decades.

Classically, a trial is run to evaluate the ability of new drugs or combinations of drugs to increase the proportion of children who are cured of their malignancy. Over the past few decades, increasing numbers of trials have been conducted with the aim of reducing therapy so that patients are cured with fewer treatment-related sequelae. During the 1980s and 1990s, the great majority of patients attending most paediatric oncology centres in the UK were entered into clinical trials. However, that period of endeavour and achievement seems now to be drawing to a close. Recently, not only in the UK but also across Europe as a result of the EU Clinical Trials Directive[2] and its associated national legislation, there has been a sudden increase in the burden of regulation which has become a major impediment to clinical trial activity.

ACUTE LYMPHOBLASTIC LEUKAEMIA TRIALS

The UK Medical Research Council established a childhood leukaemia working party in 1954 and the initial trials UKALL II, III, V, VI and VII were completed by 1980, with the latter achieving a 4-year event-free survival (EFS) of 65%.[3] UKALL VIII was the first trial to incorporate treatment resembling modern chemotherapy for ALL. At the time of its conception outcome was worse for children in the UK compared to children in the US. As a result, one of the objectives of UKALL VIII was to see if similar outcomes could be obtained using an identical protocol. To that end, the regimen was heavily based on the US CCG protocol 162. The second objective was to examine the role of daunorubicin in induction therapy. (It is intriguing that both these issues continue to occupy us over 20 years later!) The outcome of this trial was that results similar to those seen in the US could be obtained, and that whilst the addition of daunorubicin improved disease-free survival, its use was associated with more early deaths.[4] UKALL X explored the notion that post-induction intensification of therapy would improve survival further, a suggestion supported by data from the Berlin-Frankfurt-Munster (BFM) group in their series of studies.[5] Patients were randomised to receive no intensification at all, or an early module, a late module or both. The results indicated that receiving both modules resulted in the best outcome, with the greatest benefit being seen in patients perceived as being at low risk of relapse, that is, younger girls with low white cell counts at presentation.[6] UKALL XI extended the intensification idea with a third, extended, BFM-style module given relatively late (week 35) in therapy and also explored alternative methods of CNS prophylaxis. However, the overall results were not an improvement on UKALL X,[7] and the CNS protection issues became less relevant in view of contemporaneous results from the US CCG and the BFM group.

The most recently completed trial, ALL97/99, examined the roles of the steroids and thiopurines. History and habit had enshrined the use of prednisolone and 6-mercaptopurine, but it seemed possible that the alternatives of dexamethasone and 6-thioguanine might yield further increments in cure rate. The trial was closed early because of the superiority of dexamethasone.[8] Whilst 6-thioguanine conferred a significantly lower risk

Abbreviations: ALL, acute lymphoblastic leukaemia; BFM group, Berlin-Frankfurt-Munster group; CCG, Children's Cancer Group; EFS, event-free survival; ENSG, European Neuroblastoma Study Group; EORTC, European Organisation for Research and Treatment of Cancer; EUCTD, EU Clinical Trials Directive; HDM, high-dose melphalan; MHRA, Medicines and Healthcare products Regulatory Agency; MRD, minimal residual disease; NCRI, National Cancer Research Institute; NWTS, National Wilms' Tumor Study; OS, overall survival; RT-PCR, real-time quantitative polymerase chain reaction; SIOP, International Society of Paediatric Oncology; UKCCSG, UK Children's Cancer Study Group

Correspondence to: Chris Mitchell, Paediatric Haematology-Oncology, John Radcliffe Hospital, Oxford, UK; chris.mitchell@paediatrics.ox.ac.uk

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of isolated CNS recurrence, this advantage was offset by a higher rate of deaths in remission and the development of veno-occlusive disease of the liver in 11% of recipients.[9] The results of UKALL VIII were reinforced by the mid-trial finding that outcomes in the UK were again inferior to those seen in the US and Germany, forcing a redesign of the core therapy programme, although it proved possible to retain the randomised components.

By 2003 the investigators were confronted by the realisation that whilst there had been a 20% improvement in cure rate since UKALL VII, the cost of this increment was that all children were having more therapy than in the early 1980s and that there were penalties in short-term mortality and long-term morbidity. As 65% of the children would have been cured with less therapy and 15% were still relapsing, only 20% of patients were benefiting from the extra treatment. The problem was to identify the risk groups in a more specific way so that treatment could be better tailored to risk of recurrence. The usual suspects of age, sex and white cell count were joined by speed of response, assessed by inspection of the bone marrow during the induction period. These factors, however, did not give sufficient precision for further refinement. The use of real-time quantitative polymerase chain reaction (RT-PCR)-based assays enabled the accurate measurement of very small quantities (down to one cell in 100 000) of residual leukaemia and led to the concept of minimal residual disease (MRD). The current trial, ALL2003, uses the treatment strategy and regimens developed in ALL97/99 but adds stratification by RT-PCR-based assay of MRD to assess, in a prospective, randomised way, the idea of reducing therapy for patients perceived to be at low risk of relapse and intensifying further the therapy for those perceived to be at high risk. This trial is continuing at present, and the difficulties of collecting adequate marrow samples and centralising MRD assays with a quality assurance system have been overcome due to the hard work and goodwill of all trial participants and investigators. It is anticipated that recruitment will close in 2009.

WILMS' TUMOUR TRIALS

The development of therapy for Wilms' tumour is often cited as an example of the success of the multicentre cooperative approach in conducting randomised clinical trials in rare diseases. The North American National Wilms' tumour studies, initiated in 1969, have provided a clear, consistent and rational framework for treatment. These studies, together with trials carried out by UKCCSG and SIOP have succeed in refining therapy so that now most patients with Wilms' tumour are cured, mostly with minimal treatment.

The first US National Wilms' Tumor Study, NWTS 1,[10] defined groups predictive of relapse risk and began the process of rationalising therapy so that those children at least risk received little treatment whilst those at greater risk received additional therapy, as indicated by their risk of recurrence. The two subsequent studies, NWTS 2[11] and NWTS 3,[12] continued this theme, establishing a robust staging system which still remains central to the rational therapy of this tumour. Simultaneous studies conducted by UKCCSG, UKW1[13] and UKW2,[14] added to the process, in particular by refining therapy for early stage tumours and exploring the notion of delayed nephrectomy for patients with inoperable or metastatic tumours.

The SIOP group had very early adopted a rather different approach, with initial chemotherapy followed by delayed surgery at 6–8 weeks for all patients. The benefits of this regimen were that the tumour would be smaller and hence easier to resect, that the response to chemotherapy could be included in the staging system used to determine subsequent chemotherapy and that, potentially, treatment could be reduced without decreasing the chance of cure but lessening the short- and longer-term morbidity associated with chemotherapy and radiotherapy.[15–17]

The issues posed by the delayed surgical approach favoured by SIOP and the immediate surgical approach favoured by the NWTS were summarised in an editorial,[18] leading the late Jon Pritchard to propose that the UKCCSG should conduct a randomised trial to compare the two systems. UKW3, as it became, started in 1991 and ran for 10 years. Patients with non-metastatic Wilms' tumour were randomly assigned to have either immediate surgery with subsequent therapy as dictated by the NWTS staging system[12] or to have a Trucut needle biopsy to confirm the diagnosis, followed by 6 weeks of chemotherapy, delayed nephrectomy and subsequent therapy again dictated by a modified NWTS staging system. The trial demonstrated that the immediate and delayed surgical approaches produced equivalent results, but 20% fewer children in the delayed surgery group required doxorubicin or flank radiotherapy in their postoperative regimens (the two therapies that resulted in nearly all the long-term sequelae0.[19] The UK group have now joined SIOP for the current SIOP trial and preoperative chemotherapy for Wilms' tumour has become firmly established in the UK.

METASTATIC NEUROBLASTOMA TRIALS

The successes achieved with ALL and Wilms' tumour have, however, not been seen in metastatic (stage IV) neuroblastoma, the entity described by Hutchison, and despite major efforts worldwide this condition remains profoundly depressing to treat, with a high mortality rate. There is often an early and dramatic response to initial chemotherapy, with prompt regression of tumour mass and amelioration of symptoms. Sadly, despite intensive treatment, all too often the child then suffers a recurrence of the tumour which proves to be refractory to further intervention, leading to the child's death, on average only 24 months after diagnosis. However, there have been numerous trials of therapy for this condition and there are perhaps now signs that this dismal outcome may be improving although the long-term overall survival (OS) remains less than 30%.[20]

Current neuroblastoma therapy employs three main components: induction chemotherapy, consolidation with high-dose chemotherapy, and differentiation treatment using cis-retinoic acid. All three elements have been the subject of clinical trials over the past 25 years. The European Neuroblastoma Study Group (ENSG) was formed to overcome the problems posed by the rarity of the condition, and conducted its first study, ENSG1, between 1982 and 1985. This trial examined the role of myeloablative treatment with high-dose melphalan (HDM) and autologous stem cell rescue in the consolidation of response to conventional chemotherapy in children with advanced (stage III or IV) neuroblastoma. HDM was shown to improve EFS and OS in children with stage IV neuroblastoma over 1 year of age with a good or good partial response after induction chemotherapy and surgery, with a 5 year EFS of 33% versus 17%.[20] A second ENSG study, ENSG V, examined the effect of dose intensity on the efficacy of induction chemotherapy by comparing a conventionally phased regimen with a rapid one. This study showed that the rapid regimen gave a significant advantage in EFS at 5 years (30.6% vs 18.2%) and at 10 years (26.8 vs 18.2%).[21]

The third component of neuroblastoma therapy is the differentiation agent, cis-retinoic acid. Laboratory studies indicate that pharmacological doses of this agent cause differentiation of neuroblastoma cells in culture. A US Children's Oncology Group study[22] demonstrated a significant

improvement in OS and EFS for patients receiving cis-retinoic acid. This study also re-examined the question of myeloablative chemotherapy with stem cell rescue, confirming the results of ENSG 1. The best results were obtained in the group of patients who received both myeloablative chemotherapy and subsequent treatment with cis-retinoic acid.

THE EU CLINICAL TRIALS DIRECTIVE

Given the plethora of clinical trials conducted by cooperative children's cancer research organisations, and the marked and impressive improvements in outcome that have resulted from this activity, one might have expected greater government support together with legislation which facilitated this activity. Indeed, in 2001, the National Cancer Research Institute (NCRI) partners agreed that accrual into cancer trials in the UK should increase from less than 4% to at least 7.5% of new patients with cancer each year, which from a paediatric perspective was a fairly modest target.

Unfortunately, within Europe at least, new legislation has not eased the establishment of new trials or their conduct. The EU Clinical Trials Directive (EUCTD) was promulgated in 2001, with the intention, allegedly, of improving the protection of patients and the reliability of research reporting and of harmonising and increasing the competitiveness of European clinical research. Within the United Kingdom the relevant legislation is enshrined in the Medicines for Human Use (Clinical Trials) Act, 2004.[23] The directive and act increased the responsibilities of the research sponsor, and imposed a variety of other requirements regarding documentation of responsibilities, patient information, pharmacovigilance, and retention of documentation. There were early concerns that there would be an increase in costs and bureaucracy such that academic clinical trials organisations might find that their resources were insufficient to meet the demands of the directive,[24] which seem now to be borne out by subsequent experiences.

The European Organisation for Research and Treatment of Cancer (EORTC) reported in 2005 that the number of new trials had fallen from 19 in 2004 to seven in 2005 and that a third fewer patients had been enrolled in EORTC trials.[25] A review of ethical approvals for surgical and oncological trials in Helsinki[25] showed that the number of approvals in these two categories had declined from 120 in 2002 to 70 in 2005. Academic drug trials fell from 20 in 2003 to five in 2005. Simultaneously, the workload for the ethics committee increased because of a sharp rise in the number of protocol amendments from 18 to 69 and in reported significant adverse events from 16 to 183.

A very recent study from the UK confirms the early concerns of researchers and the results from Finland. Questionnaires were sent to the UK clinical trials units, and directors and senior staff were interviewed about their perceptions of the EUCTD and its impact on all stages of trial development and conduct.[26] The authors conclude that the EUCTD has increased the cost and caused delay to non-commercial cancer trials run by major public sector clinical trials units in the UK. Rather than harmonising and simplifying the regulatory environment, the EUCTD has stopped many units from running trials in international centres. Much of the criticism is directed at the Medicines and Healthcare products Regulatory Agency (MHRA), the organisation charged with policing the requirements of the EUCTD and the Medicines for Human Use Act. Of particular note are the inconsistency in advice, difficulty in getting definitive information on issues such as pharmacovigilance, the poor information on the web site, and the inability of the MHRA to state what it, itself, expects to see contained in annual safety reports.

Concerns were expressed by variety of interested organisations at the time that the directive appeared. All those concerns appear to have been justified and it would appear now that the major impact of the directive has, in fact, been to reduce the amount of clinical research in the UK. For children with cancer the effect of this directive has been appalling, so that recruitment to trials is now rapidly falling as institutions reduce the number of trials they are able to offer as a consequence of increases in costs and bureaucracy that can be attributed directly to this directive. Additionally, researcher time is being used in inspections that are poorly carried out by audit teams who seem to apply regulations inconsistently and who will not supply clear guidance about what, precisely, is required. Queries are met by the response that the requirements are laid out in the relevant legislation, yet requests for clarification of the legislation are often either ignored or else referred for a legal opinion.

Had there been a problem with the conduct of trials in the past, the necessity for the EUCTD with all its implications might have been understandable. However, as shown above, a great deal of excellent work was achieved in the past without the current burdens and with major advances in outcomes. The clinical trials unit staff interviewed by Hearne and Sullivan[26] agreed that there were already sufficient safeguards in place prior to the EUCTD with independent data, safety monitoring and ethics committees and review of significant adverse events by independent trial steering committees. It is interesting to note that the adoption of a directive by the EU Council of Ministers takes place in secret, as does the scrutiny preceding the subsequent promulgation as UK law, leading to the observation that the only countries with less open scrutiny of new laws than the UK are Cuba and North Korea![27–29]

CONCLUSIONS

At present academic clinical trial researchers will have to live within the constraints imposed by the EU directive and UK legislation with the adverse implications for trial costs and researcher time. It is to be hoped that, in time, at least some of the more nonsensical requirements will be withdrawn, or else clinical trial activity and the associated improvements in outcomes for many groups of patients, not just children with cancer, will become distant memories.

Competing interests: CM is actively engaged in recruiting patients to clinical trials conducted by the Children's Cancer and Leukaemia Group and sponsored by the University of Sheffield and University of Leicester.

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