

Acute lymphoblastic leukaemia (ALL) things come to those who wait: 60 years of progress in the treatment of adult ALL

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Summary

The UK has made a well-recognised contribution to the international effort to understand and treat acute lymphoblastic leukaemia (ALL) in adults. Work done in the UK by numerous personnel over many years has been instrumental in developing novel risk stratifications, evaluating treatment strategies for adult patients with *de novo* and relapsed disease and in making novel scientific contributions. The UK has championed and achieved very high levels of recruitment to clinical trials and, in particular, is known for success in large, investigator-initiated randomised controlled trials. This historical review charts the progress of clinical research in adult ALL from its inception to the present day.

Keywords: adult, acute lymphoblastic leukaemia, TRIALS.

In the beginning

In 1957, the Medical Research Council (MRC) set up a steering committee to evaluate different forms of treatment in cancer. The first ‘Working Party’, which included Dr (later Sir) Richard Doll, set up a factorial trial to elucidate the efficacy of mercaptopurine and different doses of corticosteroids in acute leukaemias of both myeloid and lymphoid origin, which showed that adult leukaemia was typically a rapidly fatal disease that was not greatly influenced by those methods of treatment.¹ Trials in acute lymphoblastic leukaemia (ALL), in particular, began in earnest in the early 1970s and continued to be developed by MRC ‘Working Parties’. For some years, the MRC ‘brand’ of trials was internationally respected, being synonymous with high-quality leukaemia trials from the UK. The early studies, of course, long preceded the requirement for a trial sponsor, but were administered by the Clinical Trial Service Unit (CTSU) and Epidemiological Studies Unit at Oxford, an intellectual powerhouse of statistical and trial design expertise, with input from relevant physicians. Up until the 1970s, haematologists

were generally trained as pathologists, but a change in emphasis was required as it became increasingly possible to treat diseases such as leukaemia. Anthony (Tony) H. Goldstone exemplified this new breed of professional, having trained in general medicine and haematology in Edinburgh and Cambridge, as opposed to training in ‘pathology’. He was appointed to a consultant haematology post at University College London Hospitals (UCLH) in 1976, by the departmental lead Professor Tom Pranker, a ‘physician haematologist’ within the Department of Medicine, who underscored the importance of haematologists as general physicians and had been visionary in establishing a separate department of clinical haematology. In a key opinion piece for *The Lancet*, Pranker made clear that ‘interests (of the patient) can be adequately served only by providing a cadre of haematological physicians – doctors who should have a wide background of general medical training as well as a special interest in blood disease.’² Along with Tony, Alan Burnett, H. Grant Prentice, Ian Franklin, and I. Jill Durrant were key ‘haematological physicians’ working on the MRC trials for Adult ALL. Susan M. Richards, Senior Research Fellow at CTSU was a critical statistical and intellectual contributor to both adult and childhood ALL trials, working alongside her colleague Georgina Buck, medical statistician.

You don’t always get what you want

During the MRC trials II–VII, various aspects of the basic treatment protocols for ALL were tested with generally disappointing results. Of 1470 children recruited between 1972 and 1979, <50% remained in remission at 4 years.³ The protocols of the Bayern-Frankfurt-Munster (BFM) West German group then began to be adopted for childhood use. It is hard to imagine nowadays, but blood products were not always readily available, rational use of antibiotics was often absent and expertise amongst nurses and doctors across different centres was variable, meaning that it was hard to control the morbidity and mortality of the intensified therapies. By the 1990s, survival in adult ALL had increased in 5-year disease-free survival from 5% to 38%.⁴ The main contribution of these trials so far, had been ‘in examining prognostic features in all patients and finding that age and the presence of the Ph chromosome, independent of WBC count, gender, and cell type’, were the main features for predicting outcome.

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The trials had generally included a treatment approach for both children and adults, but the approaches were managed by separate groups who did not meet together regularly. The childhood–adult age divide had been set at 15 years. The UK community strongly supported randomised trials with the potential to change practice, which has generally been a well-justified approach.

Please will you sponsor me?

The 12th MRC Adult ALL study UKALLX11/ECOG2993, opened in 1993 and was arguably the first UK adult ALL trial of the ‘current’ era. Even though UKALL10 had been designed as an intensified protocol for adults,⁵ this was a step change from UKALL10 in intensity and was the first trial to employ the sort of modified BFM-type regimen that would be recognisable to today’s generation. At the time the UKALL12 pilot study was being evaluated, Adele Fielding was a postgraduate medical trainee at UCLH and, being familiar with UKALL10 protocol, recalls being shocked at the intensity of the UKALL12 therapy being given. Individual patients from that era are still fresh in mind, who can forget seeing their case of cerebral venous sinus thrombosis or their first time negotiating with a young patient who is poignantly begging to be allowed home for the weekend? These experiences kindled a long-term desire to facilitate a move from successful but toxic ALL therapy to just successful ALL therapy.

The UKALL12/E2993 was pivotal in several ways. First, it was designed to ask important questions on the relative merits of autologous and allogeneic transplantation, both modalities that were in common use based largely on single-centre reports, each with their adherents and detractors, but with only a modest dataset underpinning their use. Humphrey Kay, who had served as secretary to the MRC’s Leukaemia Committee since its founding in 1968 had been instrumental in requesting of Tony Goldstone that these therapies were evaluated. Second, molecular studies of minimal residual disease (MRD) in adults, led by Letizia Foroni⁶ were included for the first time in the UK, which also led to the first specimen collection. Third, and critical as an example of the benefits of large international co-operations, this trial was an international collaboration with the Eastern Cooperative Oncology Group (ECOG) of the USA, brokered by Tony Goldstone and Jacob Rowe during a walk in the Black Forest. Jacob Rowe led the ECOG effort with vital contributions from Mary Tallman, Hillard Lazarus, Mark Litzow and Selina Luger, with Elisabeth Paietta co-ordinating the USA central laboratory effort. This transatlantic co-operation was important in a more general sense, helping to bring attention from the USA to the ALL studies being done in Europe and *vice versa*, another distinguishing feature of UKALL12 was that it was already well advanced by the time a Sponsor became a legal requirement. The prodigious outputs from this trial, which was the largest ever trial in adult ALL, are well-known in the community and include seminal papers on the

superiority of chemotherapy over autologous transplant⁷ and the first cytogenetic risk classification of adult ALL, led by Anthony Moorman.⁸ What is less well known about UKALL12 is how hard it was to find a suitable UK sponsor for the trial. As the CTSU Oxford did not offer trial sponsorship, Adele Fielding took up the mantle to persuade her employer University College London (UCL) to sponsor this study, having joined with Tony Goldstone to work on ALL after returning to the UK from a stint working at the Mayo Clinic. UCL eventually agreed to take over sponsorship from Tony Goldstone who was personally sponsoring the study. This, surprisingly, was legal at that time, but not ideal. Following the first Medicines and Healthcare Products Regulatory Agency (MHRA) inspection at UCL where UKALL12 was one of the trials chosen, UCL concluded that UKALL12 that had been carefully conducted and well run under the old regulations was a huge challenge to manage under the new more stringent regulations, underlining the huge changes in trial conduct that had been wrought by the European Union (EU) Directive converted into UK law as The Medicines for Human Use (Clinical Trial) Regulations of 2004. It remains very challenging for all parties to adhere to the directive when studying diseases where therapy is long and complex. The issue of adverse event reporting has been examined in detail in a commissioned report from an international panel of clinicians, clinical investigators, methodologists and regulators should the reader wish to delve further into the concerns and potential solutions.⁹

To date, UKALL12 has contributed to 53 publications. UCL has thankfully agreed to retain sponsorship of UK ALL trials and has also taken on the paediatric trials. Amy Kirkwood has supported the statistical handover from Oxford to London and UK adult ALL trials continue to benefit from her first-class input. The contributions and support of critical trial personnel also cannot be underestimated, we are grateful to numerous staff at CRUK and UCL Cancer Trial Centre for their enormous contribution to adult ALL trials in the UK.

Treat me like a child

During the conduct of UKALL12 it became increasingly clear that teenagers and young adults benefitted from being treated in a more intensive manner than hitherto; a pivotal UK paper showed a much superior outcome for patients aged 15–17 years who had been treated on the paediatric rather than the adult protocol, which at the time had overlapping age limits.¹⁰ The UKALL12 trial management team met together with paediatric trialists in particular, Nick Goulden and Ajay Vora, to agree a revised age limit for our protocols. In a cautious manner, we revised upwards from 18 to 20 years and eventually settled, for pragmatic reasons related to teenage and young adult units, on 24 years as the cut-off for childhood/adult trial enrolment. The UK National Cancer Research Institute (NCRI) Adult ALL group created a

specialist teenage and young adult team of Clare Rowntree and Rachael Hough, who worked across the NCRI paediatric and adult groups to guide and assist in the adoption of the paediatric protocols in the adult-care setting. The increasing understanding that there would not be one correct treatment for all patients with ALL, rather, alternative approaches for patients of different ages would be required, set the direction for the UK to extend its efforts to patients at the other end of the age spectrum who had largely been excluded from clinical trials. This had long been a topic of importance promoted by Steve Proctor. UKALL60+ became the first ever UK ALL study open to older patients with no upper age limit.

Is there anything there?

Monitoring of MRD in ALL allows precise quantification of small amounts of disease that cannot be detected by standard approaches. Although this can be done by flow cytometry, the detection and monitoring of patient-specific immunoglobulin heavy chain/T-cell receptor re-arrangements is the most standardised approach due to the vision and persistence of founding chair Jacques Van Dongen who began the European Study Group on MRD detection in ALL, which we now know as EuroMRD. Multiple laboratories from 25 countries across Europe, Asia, Australia, North and South America participate in a twice annual quality-control programme twice per year, contribute to the development of guidelines for the interpretation of real-time quantitative-polymerase chain reaction (RQ-PCR)-based MRD data¹¹ and collaborate on development and evaluation of new MRD strategies and techniques. Adult ALL in the UK has benefitted enormously from this co-operation. MRD has been incorporated into clinical decision-making and treatment stratification in trials and is now funded by the UK National Health Service (NHS) and carried out as standard of care, strictly according to EuroMRD guidelines. The UK NCRI Adult ALL group and Adele Fielding in particular, are very grateful for the support of the Tapner family, whose substantial donation enabled the creation of the national adult ALL MRD laboratory and the transition of MRD in adult ALL from a research-funded test to a test adopted and funded by the NHS. Based on its potential to eliminate MRD,¹² regulatory approval and UK reimbursement of the novel immunotherapy agent, blinatumomab was agreed in 2019.

What doesn't kill me makes me stronger

The UK has made a particular contribution to the study of bone marrow transplant in ALL. The results from the pioneering 'donor *versus* no-donor' analysis of the outcome of allogeneic stem cell transplant in UKALL12 showed that patients with high-risk ALL did not benefit from allograft, although there was a benefit for those with standard-risk ALL. This counterintuitive finding resulted from a treatment-related mortality that equalled the considerable reduction in

relapse risk. The main contributor to the excess toxicity in the high-risk group was age,¹³ suggesting that if the immunotherapeutic benefit of allograft were to be realised in older persons, an alternative, less toxic approach was needed, leading to the incorporation of the largest ever prospective study of a reduced intensity-conditioned (RIC) approach in adult ALL in the UKALL14 study. David Marks has been pivotal to the effort of studying RIC allogeneic stem cell transplant in UKALL14 and has already established the follow-on study, ALL-RIC study. We are also fortunate to have important additional immunotherapy approaches either approved for adults with persistent or relapsed disease, namely blinatumomab or chimeric antigen receptor T (CART) cells, which are showing strong potential for safe and effective therapy of adult ALL in early phase clinical trials. The work of Martin Pule, Claire Roddie and Karl Peggs, based at UCL, has been critical to the UK-specific effort in that regard. The emergence of numerous genetic subgroups of ALL, alongside a plethora of targeted therapies, now generates wonderful opportunities for novel trial designs, but at the same time challenges the feasibility of the academically-initiated large randomised controlled trials in defining the role of these agents.

What shall we do next?

Nowadays, ALL trials are developed via the NCRI ALL subgroup and compete for external peer-reviewed funding. We are grateful to CRUK, which has been a major funder of these sorts of clinical trials. We also have been grateful, both then and now, for the resources of the NHS, which provides the vital trial infrastructure 'on the ground' and makes large investigator-initiated trials relatively inexpensive to conduct by comparison with pharma studies. We have always been fortunate to co-operate with informed and enthusiastic local Principal Investigators in NHS centres, who are the vital backbone of ALL trial success. Numerous investigators have also stepped up to perform outstanding roles in recruiting patients, participating in trial management groups, sharing expertise on the NCRI Adult ALL group and participating in the processes of novel agent approval, Tobias Menne, Nick Morley, Andrew McMillan and Debby Yallop among them. The UK has been prescient in recognising and promoting trial entry to patients with rare diseases such as ALL as the standard approach. To that end, we in the UK have typically designed our later phase trials without stringent exclusion criteria, facilitating recruitment of 80–90% of the incident population, thus ensuring that our trial data has pragmatic, real-life relevance. Another important aspect of UK NCRI-developed trials is the critical role of patient and public engagement; the group is extremely fortunate to work with Gill Murphy in this regard.

We have completed the UKALL60+, the first ever trial designed specifically for older adults with ALL, a significantly underserved group who had largely been neglected in the

trial arena. The UKALL14 has also been completed and whilst the clinical data are being prepared for publication, the first adult ALL biobank is providing valuable material for correlative science. Younger investigators are becoming interested not just in the clinical management of ALL, but in understanding the molecular and cellular biology of the disease and developing trials which are age-appropriate and incorporate correlative science. Richard Burt, Anna Castleton, Kate Bailey and Bela Patel who have passed through the Fielding laboratory and retained an interest in ALL have all made important scientific contributions in understanding the contribution of the stromal microenvironment,^{14,15} CD20 expression, MRD and leukaemia-initiating cells.^{16,17} Drs Burt and Patel had the specific financial help and encouragement of their academic 'grandfather', Tony Goldstone, underscoring the critical importance of realising that progress is typically made by 'standing on the shoulders of giants'.

The ALL work in the UK has hugely benefited not only from UK-derived mentorship, but from the co-operation with and learning from other national groups and major figures. The publications and international profile of the UK group show how much we gained from working with the United States ECOG. We have also enjoyed a 'harmonious' and beneficial collaboration with numerous European colleagues through the European Working Group on ALL (EWALL) founded some years ago by Dieter Hoelzer and Robin Foà, a forum for co-operation and exchange of ideas. Adele Fielding is particularly grateful to be the current rotating chair of this group and still belong to European initiatives. The EWALL has led directly to some ongoing co-operative projects and will foster some excellent large data science within the EU-based Healthcare Alliance for Resourceful Medicine Offensive against Neoplasms (HARMONY).

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