**THE CHRONIC MYELOID LEUKAEMIA STORY in the UNITED KINGDOM since 1960**

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Summary

 Over the past 60 years, haematologists and scientists from the United Kingdom, notably John Goldman and Tessa Holyoake, have punched above their weight in changing chronic myeloid leukaemia from an incurable and invariably fatal disease for all, to a chronic condition where over 90% have normal life expectancy. As a result, it is now difficult to power a worthwhile phase 3 study for newly diagnosed patients. Nevertheless, important clinical questions remain.

General developments in CML from 1960 to the 1990s

 The starting year of our story for this special edition, 1960, was the year in which Peter Nowell and David Hungerford described a small chromosome in blood cells from 2 CML patients, later found to be an abnormally short chromosome 22 and termed the Philadelphia (Ph) chromosome to honour the city in which they worked (reviewed in 1). Although these 2 authors have rightly received the credit for this finding, it is interesting to note that this could so easily have been the Edinburgh chromosome, following the almost contemporary description from the Western General Infirmary in Edinburgh of a specific chromosomal abnormality in studies on 12 CML patients 2. Following introduction of Giemsa (G) -banding techniques, this seminal observation was subsequently found by Janet Rowley (Chicago) to be accompanied by an abnormal chromosome 9, where genetic material moves but is not lost 3, thus describing the first reported translocation in any human tumour. In lunchtime discussion in 2011 with a few of us, she described her recognition of this by arranging cut outs of photographs of G-banded metaphases from CML cells on her kitchen table (asking her children not to sneeze) in 1972. A decade later, Dutch investigators showed that the chromosome 9 break occurred in the *c-ABL* gene, resulting in part of that gene coming to apposition with the *BCR* gene on chromosome 22 4,5. Shortly after this, an 8.5 kilobase *BCR-ABL* fusion transcript was demonstrated 6 that encodes an abnormal BCR-ABL protein typically of 210 kiloDaltons 7, which is sufficient to drive myeloid proliferation and produce CML 8.

British clinical developments from 1960 to the 1990s

 Following an initiative by the Medical Research Council (MRC) in 1957 to examine the new modality of chemotherapy in malignancy, David Galton (BJH editor 1966-68, and later honorary Director of the MRC Leukaemia Unit at Hammersmith Hospital and my main MD examiner) was a leading figure in the creation of the MRC Working Party on Leukaemia, under the chairmanship of Leslie Witts, Nuffield Professor of Medicine at Oxford and the inaugural BSH president from 1960-62. The remit of this Working Party was to evaluate whether chemotherapy might displace radiotherapy as the mainstay of leukaemia treatment, and one of its first studies showed that in CML the alkylator busulphan (introduced by Galton around 1959) improved survival by almost a year compared with radiotherapy given in various ways 9.

 When John Goldman was appointed to the new MRC Leukaemia Unit at Hammersmith Hospital in 1971, CML was therefore incurable, with busulphan as the centrepiece of treatment. John pioneered the development of stem cell transplantation for CML, initially as autografting in blast crisis using cryopreserved buffy coat cells from earlier chronic phase 10, then in the first United Kingdom (UK) report of allografting from siblings 11 and later from unrelated donors 12, and in the recognition that T cell depletion (to mitigate graft versus host disease) is associated with an increased relapse risk 13.

 The next multicentre randomised CML study in the UK was led by Galton and Richard Peto during 1972-79, showing that early elective splenectomy did not improve quality of life or delay transformation to advanced disease 14. This was followed by CML 2, a 675 patient randomised trial of thioguanine, led by Edinburgh haematologists Pat Shepherd and Norman Allan. It showed that when added to busulphan therapy, thioguanine conferred an unacceptable level of portal hypertension and no survival advantage, and thus had no place in CML treatment 15.

 Interferon-alpha (IFN) was introduced into CML treatment by the Houston group in 1983. Although associated with troublesome side effects in ~30% of patients, early data suggested that it might produce some cytogenetic improvement and delay progression. The UK MRC CML 3 study, again led by Shepherd and Allan, compared IFN with busulphan or hydroxyurea (hydroxycarbamide) in 587 patients, and ultimately demonstrated in line with several other trials that IFN prolonged median survival by 20 months and produced cytogenetic improvement in 22%, something not seen with busulphan/hydroxyurea 16. A by-product of CML3 was its meta-analysis with 2 other studies that demonstrated a survival advantage for hydroxyurea over busulphan 17, resulting in the abandonment of busulphan (except for transplantation conditioning). In the early 1990s, a CML subgroup of the MRC Leukaemia Working Party was created, chaired by Norman Allan, to develop and run CML trials. Similar subgroups were also created for the other leukaemias, and they are now the main engine for developing and running trials across cancer, under the auspices of the National Cancer Research Institute (NCRI) which has superseded this aspect of the MRC.

Targeting BCR-ABL

 My general interest in haematological cancer stemmed from house physician days in oncology in 1979 at the Westminster Hospital, London (closed 1984). Westminster was a hotbed of transplant activity at the time (discussed elsewhere), and for 3 months I was the most junior end of the new adult transplant team headed by our Editor in Chief John Barrett, newly returned from Paris. After a year in Cambridge with Don Chalmers, an under-recognised early pioneer of computerisation in the haematology laboratory who died young in 1984, and briefly with Frank Hayhoe’s leukaemia team (BSH president 1970-71; discussed elsewhere), I took a research fellowship in 1983 with Allan Jacobs (BSH President 1974-75 and BJH editor 1975-77) in Cardiff. Allan’s major interest had been in iron metabolism (also discussed elsewhere) with Mark Worwood (BJH editor 1987-91), but I was hired to investigate the more widespread haematological derangements in what we now call refractory anaemia with ringed sideroblasts, one of the myelodysplastic syndromes (MDS). MDS became a central focus of my and the Cardiff department’s work until I moved to Liverpool in 1990 and Allan’s all too brief retirement from 1991.

 Like many others I became attracted to CML in the early 1990s because if BCR-ABL alone is sufficient to drive the disease, BCR-ABL inhibition might prove useful therapeutically. Together with local biochemist David Tidd, we worked on *BCR-ABL* inhibition *in vitro* by antisense therapeutics directed against the *BCR-ABL* fusion junction. This led to a small clinical trial of antisense purging of CML marrow prior to autologous transplantation. I first got to know John Goldman when he asked me to present our data at a meeting in 1996, at which his group showed similar antisense marrow purging studies directed against *MYB*, in conjunction with Alan Gewirtz in Philadelphia. Also at that meeting we heard for the first time the impressive *in vitro* findings of Brian Druker and colleagues in Oregon on a compound called CG (for Ciba-Geigy) 57148B 18, a tyrosine kinase inhibitor (TKI) active against *ABL*.

Clinical developments during the 1990s

 Up until the mid-1990s, we see then that the story of clinical CML studies in the UK is the emergence around 1960 of a proper trial ethos, leading to sequential internationally competitive trials on key therapeutic questions of the day. Around 1997, John Goldman took over the chairmanship of the MRC CML subgroup, and two new studies were developed and opened; CML 4 for younger patients ineligible for allografting, comparing autologous transplantation with IFN maintenance versus IFN alone, led by Ian Franklin, and CML 5 which examined IFN dose primarily in older patients, led by Pat Shepherd in parallel with the Dutch/Belgian HOVON group. But behind the scenes, John and Brian Druker were particularly active in persuading Novartis (formed by the merger of Ciba-Geigy and Sandoz in 1996) to develop CG57148B for clinical studies. In late 1999 the dramatic phase 1 data of this compound (by then called STI-571) in IFN-refractory chronic phase CML were presented 19, swiftly followed by encouraging data in more advanced disease and in each case with low toxicity. Suddenly, the randomisations in the CML4 study became unattractive, particularly once the International Randomised study of Interferon plus cytarabine and STI-571 (IRIS) opened at 12 UK sites from mid-2000, offering STI-571 (definitively named imatinib) to at least 50% of newly diagnosed patients 20, together with several phase 2 studies of imatinib in other settings of treatment failure. Nevertheless, despite the dawn of this modern era of TKI therapy, Pat Shepherd completed CML5, demonstrating with HOVON colleagues that the hitherto widely used high doses of IFN could be decreased without loss of response 21.

British scientific developments since 1990

 In addition to innovative transplant studies, John Goldman also established at Hammersmith many laboratory studies of CML, notably aided by Myrtle Gordon (CML interactions with marrow stroma), Junia Melo (signalling of BCR-ABL and related proteins) and Jane Apperley (studies allied to transplantation, who ultimately succeeded him in 2004). Many of the overseas visitors to his department have themselves become international figures in CML, notably Tim Hughes (Adelaide, Australia), Andreas Hochhaus (Heidelberg then Jena, Germany), Francois-Xavier Mahon (Bordeaux, France) and Michael Deininger (Salt Lake City, USA). Unlike IFN, TKIs produce complete cytogenetic remission in most patients, and more sensitive techniques are required to monitor response to TKI treatment. One important development by Nick Cross at Hammersmith was of quantitative polymerase chain reaction (PCR) molecular techniques to measure *BCR-ABL* transcripts 22. This is now generally used as the mainstay of monitoring treatment response, and he and John Goldman led the emergence of International Standardisation for *BCR-ABL1* transcript measurement and the development of quality control programmes across the UK 23 and Europe. Other important molecular work in the 1990s was characterising the breakpoints in *BCR-ABL1* and their relevance to disease progression by Ken Mills (former Scientific Secretary of BSH) in Glasgow then Cardiff 24, 25.

 Tessa Holyoake’s interest in CML arose from initial work in marrow culture with Ian Pragnell in Glasgow, consolidated by a research fellowship in the Eaves laboratory in Vancouver, another world-class centre of CML research focussed on primitive CML cells. I first met her at one of the excellent biennial International Symposia on CML in the late 1990s. These informal and friendly meetings were set up by John Goldman with Angelo Carella (Genoa, Italy) and located on the Italian Riviera until becoming too large for venues there, evolving into the annual European School of Haematology CML meetings. Tessa and I became good friends and colleagues, and it was no surprise that on her return to Glasgow she rapidly set up a laboratory, later named the Paul O’Gorman Leukaemia Research Centre, that contributed much to the scientific understanding of how TKIs work. A notable contribution was the realisation that TKIs do not kill primitive CML cells 26, 27. The remainder of her career, cut short in 2017, was focussed on curing CML by augmenting TKIs to eradicate these persisting primitive CML cells, including innovative early clinical trials discussed in the following section. In doing so she formed strong collaborations with many international CML groups and attracted many now active in CML, notably Mhairi Copland who succeeded her as head of the Paul O’Gorman centre, Heather Jørgensen, David Vetrie and Vignir Helgasson, all of whom remain in Glasgow.

 Other UK scientific and translational work has helped to understand the biology of CML in recent years. Brian Huntly (Cambridge) identified deletions on chromosome 9 adjacent to ABL and that these may be adverse prognostic features 28, and later derived a mouse model as a platform to study the events leading to disease progression 29. Hammersmith Hospital has the largest CML practice in Europe, and there Jane Apperley, John Goldman and colleagues have made many important translational observations, notably that the early molecular response to treatment is predictive of long term outcome 30 and on the risks of TKI to the unborn child. My own group identified that imatinib is actively transported into cells by the organic cation transporter SLC22A1 31, the expression of which may be clinically relevant 32, though active uptake may be less important for newer TKIs 33. The work of Adam Mead and colleagues (Oxford) on single cell analysis of the genome, transcriptome, epigenome and proteome in CML has altered understanding of clonal heterogeneity and how this might change in response to treatment and during disease evolution 34. Importantly, these techniques may be clinically relevant in predicting disease evolution and are potentially portable to other malignancies 35.

Clinical developments in the UK in the TKI era

 Unfortunately, the strong UK track record of large phase 3 CML studies becomes rather less impressive from ~2000 onward. This is partly because imatinib, and later the second generation TKIs dasatinib and nilotinib, were at first only accessible within pharmaceutical company-sponsored trials, limiting the development of academic-led studies and confining access to these drugs to ~10 UK sites that Pharma deemed worthwhile to open. Since imatinib and IFN have additive and synergistic anti-proliferative effects *in vitro,* the phase 1/2 PISCES (PEG-Intron and STI571 Combination Evaluation Study) study, led by Stephen O’Brien, examined escalating combinations of imatinib and pegylated IFN. In 49 patients (32 newly diagnosed), after 6 months of treatment the complete cytogenetic response rate was 36.7% (n=22) overall and 41.2% (n=14) in the newly diagnosed 36. These somewhat immature data were presented at the American Society of Hematology (ASH) 37.

 The STI571 Prospective International Randomised Trial (SPIRIT, subsequently named SPIRIT1) trial, also led by Stephen O’Brien, was originally conceived as the UK component of a ~3000 patient study also taking place in France and Germany, to compare higher doses of imatinib (800mg in the UK) with its standard dose (400mg daily) either with or without IFN. UK SPIRIT recruited 258 patients, but potential allocation to IFN became unpopular, and the trial closed, despite successful French 38 (636 patients) and German 39 (1014 patients) parallel SPIRIT trials. Its successor was SPIRIT2, which recruited from 2008-13 and completed in 2018, also led by Stephen O’Brien. This randomised 814 newly diagnosed chronic phase patients 1:1 between dasatinib and imatinib at standard dosage. No difference was seen in 5 year event free survival (the primary endpoint) between the two arms. This was presented at ASH in 2018 40, and the definitive publication with the main results of the study is eagerly awaited, though ‘bolt-on’ scientific studies are recently published or due for imminent submission 41-43. Its planned successor study, SPIRIT3, was centred on second line ponatinib for patients with BCR-ABL1IS >10% after 3 months of treatment, but this was abandoned following recognition of the high rate of cardiovascular problems with ponatinib.

 At present there is therefore no academic-led first line study available in the UK. This stems not so much from lack of ideas, but rather because the excellent results of first line imatinib (and second line TKIs for imatinib failure) mean that the numbers of patients needed to demonstrate superiority of a novel strategy for any clinically relevant endpoint is too large to be feasible within reasonable timescales. However, in the recent past the UK has run several successful studies in clinically relevant settings other than newly diagnosed chronic phase. CU-GIMI (pun intended) was a multicentre study led by Tessa from Glasgow, examining whether incorporating G-CSF or briefly interrupting imatinib treatment might recruit quiescent primitive CML cells into cycle and thus render them amenable to TKI killing. No significant advantage was seen for either of the experimental arms over continuous imatinib alone, though this was a small study that might have missed small but clinically relevant effects 44. The DESTINY study, led by myself, initially halved TKI dosage for 12 months and then completely discontinued treatment in patients with excellent molecular responses to at least 3 years of TKI therapy. Patients in stable MR4 (BCR-ABL1IS ≤ 0.01%) had a 3 year recurrence free survival of 72%, which is better than comparable studies and might be related to the gradual de-escalation. DESTINY also included patients in stable MR3 (BCR-ABL1IS ≤ 0.1%) but not consistent MR4, and their 3 year recurrence free survival was 36% 45, 46. The CHOICES study was the brainchild of Tessa and Glasgow colleagues, arising from the observation that imatinib induces autophagy in primitive CML cells, and this can act as a protective shield; thus autophagy inhibition might be therapeutically useful in TKI resistance. The trial randomised 62 patients refractory to TKI treatment to imatinib plus the autophagy inhibitor hydroxychloroquine (HCQ) versus imatinib alone, and showed a trend for a greater reduction of BCR-ABL1 levels in the HCQ containing arm at 24 months (though not at the primary endpoint time of 12 months), suggesting autophagy inhibition may be of clinical value 47. The MATCHPOINT trial, initiated by David Marin (Imperial) and myself but taken forward by Mhairi Copland in Glasgow, showed that in blast crisis, ponatinib added to initial chemotherapy and as maintenance was both feasible and without appreciable additional toxicity at the dose of 30mg, and should be considered especially in patients who progressed whilst on other TKIs. The findings were reported at ASH 2019 48 and a manuscript is in preparation. Finally, a study of adding various novel agents to a TKI control arm is due to open imminently. Known as TASTER and led by Mhairi Copland, the design is similar to the LI-1 strategy for AML, and will initially test tazemetostat and idasanutlin, targeting EZH2 and p53 respectively, in patients resistant to at least 2 TKIs and ineligible for transplantation. Graeme Smith (formerly Leeds), Jane Apperley, Mhairi Copland and colleagues have recently published a BSCH guideline for current CML management orientated to UK practice 49, which builds on and extends many of the recent European LeukemiaNet recommendations 50.

Current status and future directions

 Because of the dramatic improvement in outlook brought by TKIs, clinical and laboratory research in CML is now less attractive to those that fund leukaemia research, not just in the UK but internationally. However, three broad problems remain. Firstly, many patients endure low level side effects from TKIs, and we need a better understanding of how to mitigate and manage these, especially the increased risk of vascular events with nilotinib and ponatinib 50, 51. Secondly, the outlook for blast crisis remains poor (median survival ~10 months). Improved understanding of the molecular events accompanying progression is needed, and a recent report using integrated multiomics to study chronic phase and blast crisis samples (some paired) suggests that many lesions arising at transformation may relate to the polycomb repressor complex (PRC), altering the expression of a wide range of genes 52. At initial diagnosis, although the available scoring systems and certain chromosomal abnormalities can identify those at higher risk of death from CML or progression, they are not powerful enough to underpin a different treatment strategy, and newer prognostic markers are needed. Here the work of Claire Lucas (until recently with my group but now at Chester Medical School) on Cancerous inhibitor of protein phosphatase 2A as a biomarker of progression is of interest 42, 53. Thirdly, many though not all patients are keen to stop treatment, but despite many studies of treatment discontinuation, we cannot reliably predict the ideal time to do so for individual patients, though serial monitoring of BCR-ABL1IS levels may be helpful 54. Progress in these areas may well require international co-operation, and the UK’s strong recent track record in international CML projects must continue despite the obstacles posed by imminent departure from the European Union.

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