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Leopoldo, 61 years old, is an IT engineer and loves spending time sailing. Leopoldo lives with haemophilia B.

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Due to the long half-life of Refixia, the frequency of dosing in the post-surgical period may be extended to once weekly after the first week until bleeding stops and healing is achieved. *Intravenous use.* Intravenous bolus injection over several minutes after reconstitution of the powder for injection with the histidine solvent. The rate of administration should be determined by the patient's comfort level up to a maximum injection rate of 4 ml/min. **Contraindications:** Hypersensitivity to the active substance, or to any of the excipients, or to hamster protein. **Special warnings and precautions for use:** Hypersensitivity Allergic type hypersensitivity reactions are possible with Refixia. The product contains traces of hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. In case of shock, standard medical treatment for shock should be implemented. Inhibitors After repeated treatment with human coagulation factor IX (rDNA) products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing. There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX. 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Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breastfeeding is not available. Therefore, factor IX should be used during pregnancy and lactation only if clearly indicated. **Undesirable effects:** Common (≥ 1/100 to < 1/10): nausea, pruritus (terms pruritus and ear pruritus), fatigue, injection site reactions (injection site pain, infusion site pain, injection site swelling, injection site erythema and injection site rash). Uncommon (≥ 1/1,000 to < 1/100): hypersensitivity, palpitations, hot flush. Unknown (cannot be estimated from the available data): anaphylaxis, inhibitors. Hypersensitivity or allergic reactions have been observed rarely with recombinant factor IX products and may progress to severe anaphylaxis (including shock). In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors. Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction. The Summary of Product Characteristics should be consulted for a full list of adverse reactions.

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Refixia® 500 IU	EU/1/17/1193/001	£1,221.50
Refixia® 1000 IU	EU/1/17/1193/002	£2,443.00
Refixia® 2000 IU	EU/1/17/1193/003	£4,886.00

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* Adolescents and adults with haemophilia B treated once weekly with Refixia® 40 IU/kg are predicted to have a FIX activity higher than 40% for 130 hours out of 168 hours, equal to approximately 80% of the week.[2]

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1. Refixia® Summary of Product Characteristics.
2. Tiede A et al. Haemophilia 2017;23(4):547-555.
3. Negrier C et al. Haemophilia 2016; 22 (4): 507-513.
4. Collins PW et al. Blood 2014; 214 (26): 3880-3886

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Developments over the last 60 years in diffuse large B-cell lymphomas

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Summary

At the time of the formation of the British Society of Haematology diffuse large B-cell lymphoma was not recognised as a specific entity and was included in the category of 'large cell' or 'aggressive' lymphomas. These were fatal in 95% of cases. Today the cure rate in adults entered into clinical trials is ~70% and a large number of British physicians have contributed to this progress.

Keywords: diffuse large B-cell lymphoma, biology, classification, treatment.

Personal introduction to haematology and the lymphomas

I qualified in medicine from Cambridge University and the Middlesex Hospital Medical School (MHMS) in the summer of 1975, and my interest in haematology came about 6 months earlier, just before the pathology final examinations that examined all aspects of haematology. With a group of friends, I had spent a lot of time playing poker at the expense of attendance at the revision lectures, and as the examinations approached, we regretted our folly. Fortunately Sam Machin, whom I later worked with for >30 years, came to our rescue. Sam was a Senior House Officer (SHO) in haematology and he agreed to give our wayward group four seminars covering the whole of haematology. These seminars were didactic in nature and incredibly informative. I marvelled then, and since, at Sam's ability to see complex issues in simple black-and-white terms. All of the card school passed our pathology examinations and Sam's teaching also influenced my choice of first house job. This was 3 months neurology and 3 months with Dr Peter Ball, a gastroenterologist and general physician who also looked after the in-patients receiving chemotherapy for acute leukaemia, a situation echoed in many UK hospitals of that time. Subsequently, I was an SHO in haematology at the Hammersmith Hospital. The haematology department had been created by Sir John Dacie and although he had retired, he was often still present. Also there, as Director of the Medical Research Council (MRC) Leukaemia Unit, was David Galton, who had been a pioneer in the use of chemotherapy for leukaemia in the 1940s and 1950s. It was a privilege to have brushed up against these 'greats' of modern British haematology. At the bedside the three consultants that I mainly worked for were Ted Gordon-Smith, John Goldman and Danny Catovsky. All three had in common, a love of science and the desire to translate scientific advances into patient benefits. They were entirely responsible for their own patients, a situation that made me realise that haematology was going to be at the forefront of clinical medicine and not just a laboratory discipline. Most importantly, I learned from Ted Gordon-Smith that although the situations haematologists had to deal with were often very sad, the camaraderie that could be engendered within a close team, made it still possible to have great fun. I thought then that I would become a haematologist, but I first became a medical registrar at University College Hospital (UCH), believing that a solid foundation in clinical medicine was a prerequisite to becoming an effective clinical haematologist.

By this time I had also decided that I wanted to pursue a research-based career. A 1-year locum haematology lecturer's post became available at University College London (UCL) with Professor Ernie Huehns, an eccentric man with great intellect and generosity of spirit, and I seized this opportunity. One of the remits of this post was to assist Tony Goldstone, a young consultant haematologist at University College Hospital (UCLH), to set up an autologous bone marrow transplant programme (ABMT). My role was to establish stem cell cryopreservation and to write the protocols for patients with relapsed and resistant acute leukaemia and lymphoma. I am still astonished at my good fortune to have been given such responsibility at this early stage of my career and for this I will always be grateful to Tony and Ernie. As part of the cryopreservation quality control I needed to be able to grow haemopoietic progenitor cells *in vitro*, and I was taught to do this by Martin Rosendaal who had a stem cell laboratory at UCL. I was then very

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fortunate to meet Peter Beverley who ran the human tumour immunology group at UCL/UCLH and was at the forefront of making monoclonal antibodies to human cells, particularly T cells. We used combinations of antibodies to isolate human haematopoietic progenitor cells for the first time and I obtained a Welcome Trust Research Training Fellowship to continue this work beyond the tenure of the locum lectureship, and then an MRC Travelling Fellowship to work in David Nathan's laboratory at the Dana Faber Cancer Institute in Boston, MA, USA. David Nathan was inspirational. I returned to the UK where I obtained a Senior Lecturer and Honorary Consultant Haematologist post at the Middlesex Hospital, which enabled me to develop a clinical practice and to continue my laboratory research at the nearby UCL. My appointment was somewhat controversial as I had not completed my formal training and had not taken the MRCPath examination.

When I started at the MHMS I thought that my major clinical focus would be acute myeloid leukaemia (AML) as this disease was most closely linked to my laboratory research, but I recognised that the lymphomas were the diseases where high-dose therapy and ABMT was most likely to make a contribution. I became a member of the lymphoma team run by Dr Tony Jelliffe and Dr Gillian Vaughan Hudson, and I was able to benefit greatly from their knowledge and experience. Tony Jelliffe was a radiotherapist who specialised in the treatment of lymphomas, and with a group of friends had, in 1970, established a lymphoma trials group called the British National Lymphoma Investigation (BNLI). In 1988, Tony Jelliffe retired and my name appeared on the door as the lead consultant for the lymphoma clinic. I also later inherited his role as Director of the BNLI and as the President of Lymphoma Action (then called the Hodgkin Disease Association), a national patient centred advisory and support group. From that time onwards I realised that, through being in the right place at the right time, I had become a lymphoma specialist. My major laboratory research, however, continued in haematopoiesis and AML, and I have continued to work on AML in collaboration with Professor Rosemary Gale for >30 years. This divergence between my clinical interest and laboratory research focus is not something I would ever recommend, but having this breadth has been immensely enjoyable and rewarding.

Developments in Lymphoma

This review focuses on diffuse large B-cell lymphoma (DLBCL) because it is the most common type of non-Hodgkin Lymphoma (NHL), and the progress in this entity mirrors that in lymphoma as a whole. DLBCL is usually said to represent about one-third of all cases of NHL, but data from the Haematological Malignancy Research Network in Yorkshire and Humber suggests that in the UK, at least, it is nearer to one half [National Institute for Health and Care Excellence (NICE) Guideline ng52, 2016].

Biological and pathological advances

Over the last 60 years understanding of the biology of NHL has increased dramatically paralleled by changes in lymphoma classification. Significant contributions were made to lymphoma classification by UK histopathologists, among whom were Mike Bennett and colleagues who developed the BNLI lymphoma classification,[3] which was a major foundation of the 'working formulation' (National Cancer Institute 1982),[6] and was widely used for over a decade. This formulation was intended as a 'translation tool' and although it had significant shortcomings as a classification, being totally based on morphology and ignoring other biological features, it did greatly facilitate international comparisons. These histopathologists also led the way in performing expert central review of all biopsies from patients entered into the BNLI and later UK national lymphoma studies, an activity that was continued unstintingly by Ken MacLennan and subsequently Andrew Jacks in Leeds. Peter Isaacson, a colleague at UCL who is internationally renowned for his pioneering work on of mucosa-associated lymphoid tissue (MALT) lymphomas,[40,41] was a leading figure in the International Lymphoma Study Group (ILSG) and in 1994 the ILSG published the Revised European American Lymphoma (REAL) classification, which integrated morphological, immunological, cytogenetic and molecular features.[21] This was a major achievement at both a scientific and a political level, and formed the basis of the World Health Organisation (WHO) lymphoma classification.[23] The entity of DLBCL was now fully accepted.

Jude Fitzgibbon, Andrew Lister and colleagues at St Bartholomew's Hospital, London, UK have made notable contributions to the understanding of the molecular basis of the transformation of follicular lymphoma to DLBCL[7,30] but most of the advances in the molecular understanding of DLBCL have emanated from the USA, particularly from the laboratories of Staudt at the National Cancer Institute (NCI) and Shipp at the Dana Faber Cancer Institute. In 2000 Staudt's group demonstrated heterogeneity of DLBCL by gene expression profiling (GEP), with identification of germinal centre B cell (GCB)-like and activated B cell (ABC)-like lymphomas, as well as a third unclassifiable group.[1] ABC, but not GCB lymphomas, were shown to be associated with 'chronic active' signalling from the B-cell receptor leading to nuclear factor κ-light-chain-enhancer of activated B cells (NFκB) activation.[44] More recent studies integrating GEP, analysis of genetic structural change including copy number variation and analysis of the mutational landscape have identified far greater genetic complexity.[8,42] The study reported by Wright *et al.*,[42] identified six molecular clusters of DLBCL, a further small group with composite genetic subtypes, and a group representing over a third of all patients with DLBCL, which could not be categorised These clusters differ in their downstream biochemistry and may require different therapeutic approaches.

Clinical progress

Standard-dose therapy. By the 1960s about half of the patients with infrequent Stage I large cell lymphomas were curable with high-voltage radiotherapy. Chemotherapy for more advanced disease was largely monotherapy and was essentially palliative. This changed following advances made in childhood acute lymphoblastic leukaemia (ALL). Using the leukaemic L1210 mouse model, Skipper formulated the log-kill hypothesis, which stated that a given dose of chemotherapy kills the same fraction of tumour cells regardless of the size of the tumour rather than killing a constant number of cells. This implied that repeated courses of chemotherapy would usually need to be given to have a chance of eliminating every malignant cell, the interval between courses would need to be as short as possible in rapidly growing tumours to prevent inter-cycle regrowth and therapy would need to be continued beyond the attainment of complete remission.[37] Furthermore, he showed in the mouse model that combinations of chemotherapy drugs with different mechanisms of action achieved the best chances of cure. In pioneering clinical studies Frei and Freireich at the NCI then applied these principles to the treatment of childhood ALL and with the four-drug VAMP regimen [vincristine, hydroxydaunorubicin (adriamycin), methotrexate and prednisone] they were able to cure a significant proportion of children.[16] A similar approach was adopted for Hodgkin lymphoma with the MOPP regimen [mechlorethamine, vincristine (oncovin), procarbazine, prednisone][14] and in 1976 McKelvey and colleagues published encouraging results in NHL with a four-drug regimen incorporating Adriamycin, probably the most potent chemotherapeutic agent in NHL. This CHOP [cyclophosphamide, hydroxydaunorubicin (adriamycin), vincristine (oncovin), prednisone] regimen[28] was adopted worldwide for the treatment of histologically aggressive NHL.

Attempts to improve upon CHOP followed with the addition of one or more drugs to this regimen and the shortening of the period over which chemotherapy was administered. Major improvements were reported from single centres. Optimism abounded, but the high hopes were soon dispelled by the results of a randomised controlled trial comparing CHOP with m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone), ProMACE (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide)-CytaBOM (cytarabine/bleomycin/vincristine/methotrexate) and MACOP-B [methotrexate, doxorubicin (adriamycin), cyclophosphamide, vincristine (oncovin) prednisone, and bleomycin], showing that survival was similar with all four regimens.[15] In the UK two randomised trials comparing CHOP with alternative so called third-generation regimes were carried out with no overall survival improvement.[5,26] The important lesson was that apparently excellent results from single-centre studies may be due to patient selection, which is often unrecognised and dependent on referral patterns, rather than to therapeutic advances. Furthermore, inadequate attention had been paid to the impact of time on patient outcome. Although initially CHOP had resulted in 5-year overall survivals of just over 30%,[11] within a decade or so this had risen to ~50%.[15,18] It is informative to consider why such a large improvement should have occurred. Improvements in supportive care and familiarity with the regimen played a part, but most importantly there were fundamental changes in attitude. When I became a lymphoma specialist many oncologists treated all types of cancer and it was not uncommon to see patients who had probably failed initial therapy because they had developed severe sepsis early in the course of their treatment, and had subsequently been given reduced chemotherapy doses to try and prevent sepsis recurring. Increasing specialisation helped to reduce this practice, and an important factor, I believe, was that lymphoma care was increasingly undertaken by physicians who also looked after patients with acute leukaemia. Leukaemia doctors came from the tradition where the only good antibiotic in neutropenic sepsis was daunorubicin! Also there was a change in the attitudes of intensivists. Many had displayed a reluctance to admit patients with cancer to the intensive care unit (ICU), but this reticence was swept away by the realisation that many patients with lymphoma would get out of the ICU, out of hospital and go on to live a normal lifespan. These changes were formally enshrined in 1995 by the Callman–Hine report to the Chief Medical Officer in England and Wales, which recommended the concentration of cancer care into the hands of site-specialist multi-disciplinary teams.

One of the problems with the second- and third-generation regimens, as they were called, is that the addition of extra drugs and shortened intervals between drug administrations was often at the cost of lower cumulative doses and dose intensities of the most effective drugs in the regimen.[18] Taking this into account the German collaborative group (DSHNHL) based their trial designs on what they called the 'effective dose approach'[22] and for rapidly growing lymphomas (defined by the surrogate marker of a raised lactate dehydrogenase level), they showed that CHOP time intensification, giving the same CHOP chemotherapy every 2 weeks rather than every 3 weeks, resulted in improved survival without significantly increased toxicity.[32] However, by the time this trial was published the Groupe d'Etudes des Lymphomes d'Adulte (GELA) had shown a major improvement in the outcome of elderly patients treated with rituximab in addition to CHOP[9] and the benefit of rituximab was subsequently demonstrated in virtually all B-cell lymphomas. Long-term follow-up of the GELA study showed an R-CHOP associated improvement in survival of ~15%.[10] The question now was whether there was any benefit to time intensification in the rituximab era. The UK trial of 1080 adult patients of all ages, led by David Cunningham,[12] revealed that there was no difference in outcome between 2 and 3-weekly CHOP, and 3-weekly CHOP remains the most commonly used regimen worldwide. The overall survival at 5 years for all patients

exceeded 70%. More recently trials have addressed the addition to R-CHOP of drugs that block the NFκB pathway, for the treatment of ABC lymphomas.[13,43] The results with the addition of the Bruton tyrosine kinase inhibitor, ibrutinib, are encouraging in younger patients[43] and the results of further trials are awaited with great interest.

High-dose therapy and stem cell transplantation. My initial interest was the development of high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) for patients with relapsed and resistant lymphomas. We first developed a high-dose combination chemotherapy regimen containing BCNU, etoposide, cytosine arabinoside and cyclophosphamide (BEAC).[2] We considered a combination of drugs with largely non-additive side effects (apart from myelosuppression) to be essential if a significant escalation of anti-tumour activity was to be achieved, and the mathematical model developed by Goldie and Coldman[17] further suggested that drug-resistant disease would almost certainly emerge with single-drug use. However, others preferred the use of monotherapy particularly high-dose melphalan and at an international autografting meeting organised at UCL by Tony Goldstone, a decision was made to merge both approaches by substituting melphalan for cyclophosphamide in the BEAC regimen. More than 35 years later, BEAM is still the most frequently used HDT regimen. Our initial studies made it clear that HDT approaches were only successful in patients with DLBCL who had failed front-line therapy, if they were still chemosensitive to standard dose salvage regimens[19] and 6 years later the randomised PARMA trial confirmed that in this chemosensitive population HDT and ASCT resulted in significantly improved outcomes.[33] By the mid-1990s, bone marrow was being replaced by granulocyte-colony stimulating factor (G-CSF) mobilised peripheral blood as a source of stem cells (PBSC)[39] and together with German investigators we demonstrated the benefits of PBSC in a randomised trial.[35] The question posed by many was whether HDT consolidation should be performed in high-risk patients during first remission. A UK randomised trial found no benefit for such an approach[27] and a joint trial between UK and Swiss investigators was stopped early because no benefit of the so-called high-dose sequential chemotherapy was apparent.[4]

In some patients PBSC could not be harvested and others relapsed after an ASCT. The results of allogeneic bone marrow transplantation with myeloablative conditioning in these situations were not encouraging due to high-level toxicity. Stephen Mackinnon was at the forefront of introducing reduced-intensity transplantation into the UK and with an informal collaborative group made some striking advances. In a cohort of 48 consecutive patients with aggressive NHL, who had failed a median of five previous regimens, including ASCT in 69%, the overall survival at 4 years was 47%.[38]

Chimeric antigen receptor T cells. Chimeric antigen receptors (CARs) were first described in Japan and Israel in the late 1980s,[20,25] but the first report of the successful clinical use of anti-CD19 CAR-T cells in a patient with lymphoma was not until 2010.[24] Two products (and a third expected) are now licensed for DLBCL that is refractory to two or more lines of treatment, with long-term survival of about 30–40%.[29,36] In the UK, trials with a 'UCL-in house' CAR and a dual CD19/22 specificity CAR, both developed by Martin Pule, are in progress.[31,34] It is conceivable that better results will occur if CAR-T-cell therapy is used earlier in the course of the disease and could replace the use of ASCT.

Future challenges

One of the major challenges is to translate the advances made in lymphoma biology into large-scale patient benefit. A consensus needs to be achieved around which molecular subclassification of DLBCL should be universally adopted and consideration may have to be given to far greater laboratory centralisation outside of clinical trials. Furthermore, the need to identify specific molecular subtypes will be driven by the development of novel therapies that are more effective in such specific entities, and this is difficult to predict. What is clear is that a more personalised approach to the treatment of DLBCL is inevitable and this creates the second major challenge of how to carry out large enough trials to prove the superiority of novel approaches in the smaller lymphoma subtypes. Many of the UK trials have involved collaborations with trials groups from other countries and this will have to increase. A third challenge relates to the design of future trials. The increased standards now demanded in all trials, means that they have become extremely expensive and there are limited non-commercial funds available. The control of trials is increasingly in the hands of the drug companies and although they also wish to improve outcomes, they have the additional need to make profits. A drug company will nearly always prefer to test a combination of two drugs that they own rather than one of their drugs with one from another company, often regardless of the scientific rationale. Maintaining independence of the collaborative trial groups has never been more important or more difficult; they must not just become effector arms of industry. A further challenge relates to the cost of new treatments and this is perhaps best exemplified in DLBCL by the immediate cost of CAR-T-cell therapies. There is no doubt that over time the cost of any given therapy will fall but the initial cost, necessary to recoup drug development costs, is prohibitive in many economies. There is no simple answer to this dilemma.

Conclusion

There has been huge progress in the last 60 years in the biological understanding and management of the lymphomas and it is has been a privilege to be a lymphoma specialist during the latter part of this period.

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