A Summary of the

11th National CML Patient Seminar

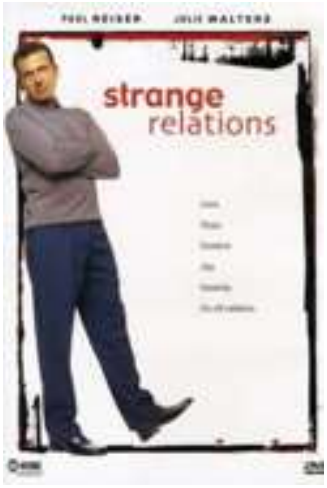
November 17th, 2012

The Glasgow Hilton, William Street, Glasgow, Scotland

BBC Scotland filmed the proceedings and interviewed individual patients for a possible documentary on rare diseases and access to innovative therapies through the NHS.

10am

The day started with a welcome from Professor Richard Clark of the Haematology Department Royal Liverpool University Hospital, with an overview of the days agenda. Professor Clark went on to contextualise the current situation regarding optimal therapy available for CML in chronic phase by using the 2001 ‘made for TV’ film called 'My Beautiful Son' (UK), 'Strange Relations' (US), as an example of just how far treatment has come over the last twelve years.



I saw this film some years back, just after my own stem cell transplant, and was highly amused at the idea that his birth mother turned out to be a close enough HLA match to be a suitable donor and nearly cried with laughter when I saw both of them (Julie Walters played his birth mother) being wheeled in to an operating theatre (!) side by side, holding hands across the gap between the operating trollies - presumably so a team of surgeons could transfer her bone marrow directly into his! Not a haematologist in sight, no mention of the unlikely situation that a parent would match an offspring closely enough to act as a donor, let alone the need for a week of chemotherapy and/or total body radiation in order to deplete his diseased marrow of Leukaemic cells.

39 year old Jerry Lipman, a wealthy New York psychiatrist, he devastated by his sudden diagnosis with leukaemia. An only child, he tells his mother, who confesses that he is adopted and his birth mother is actually a teenager from Liverpool in the UK. He sets out to search for his *birth mother as a possible donor* so he can undertake a bone marrow transplant, the only hope for his survival. (My italics)

However, it was a good vehicle for the introduction of the real situation for at least one kind of Leukaemia – CML, and the 'revolution' in therapy since imatinib became 1st line therapy a little over 10 years ago.

Prof.Clark was keen to point out, that he no longer recommends transplant for any patient diagnosed with chronic phase CML and is unlikely to do so other than in those rare and complex cases resistant to all available TKI therapies and those with blastic transformation. In other words in rarer and more complex cases.

10.15 am

Dr. Lindsay Mitchell of Monklands District General Hospital presented an in depth overview of CML, its stages and how it would evolve without therapy.

Patients often present to their GP with one or more of the following symptoms:

- Left sided pain/enlargement of spleen
- Unexplained fatigue
- Night Sweats (caused by high white cell count)
- Unexplained weight loss
- Priapism- a very rare presentation in men where there is a sustained and very painful erection and which requires urgent attention. She mentioned that in her own practice she had only ever seen one patient present with priapism caused by CML.

50% of patients have an abnormally high white blood cell count and/or other abnormal blood cell counts.

More patients are being diagnosed early as many are now picked up the requirement to have by routine blood tests for other purposes such as for health insurance or employment requirements, as well as those referred by opticians who detect possible abnormalities during routine eye examinations.

Rare

CML remains a rare disease with an incidence of 1-2 people in every 100,000 per population each year. The rate of incidence is fairly even throughout all populations globally.
In the UK this means there are between 500 -1000 new cases diagnosed each year, with slightly more men than women, and a median age of 55 years.
It is an 'acquired' chromosomal abnormality, i.e. it is ***not*** inherited.

Diagnosis

The GP will refer a patient to either an expert centre for haematology or a general hospital haematology department both of which will perform a detailed blood analysis.
FBC (full blood count) - 300 cells will be looked at under the microscope. The number of platelets and leukocytes, the % of eosinophils, basophils etc. and blasts will be counted manually and calculated. Bone marrow biopsy and/or aspirate will also be performed.

PCR will also be performed at this stage although it is unlikely to be helpful at this stage other than to quantify crudely the % ratio of the abnormal BCR-ABL gene to the normal ABL gene.

The Philadelphia (Ph) Chromosome.

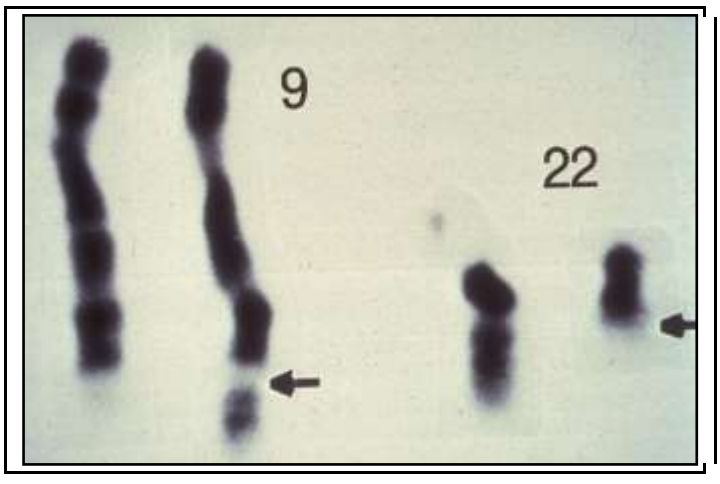


Figure 1 : The Philadelphia chromosome
Discovered in 1960, the diagnostic karyotypic abnormality for CML is shown in this picture of the banded chromosomes 9 and 22. Shown is the result of the reciprocal translocation of 22q to the lower arm of 9 and 9q (c-abl to a specific breakpoint cluster region [bcr] of chromosome 22 indicated by the arrows).

Historical context of therapy:

Arsenic (aka Fowlers Solution);

Radiation therapy; Chemotherapy: Busulphan

Hydroxycarbamide (aka Hydroxyurea)

Interferon Alpha

Stem Cell Transplantation

Post 2000 and the advent of Targeted Therapy

Since the late 90's early 2000 and the development of imatinib the overall prognosis of CML has changed dramatically.

Dr. Mitchell showed a slide of how matinib/Glivec works by fitting into the ATP binding pocket thus effectively flicking the 'on' switch to 'off'. This causes the PH+ cell to die (apoptosis).

IRIS Study = International Randomised IFN vs STI571

In 2000 the 'expanded access trials' for newly diagnosed CML in chronic phase opened at several sites internationally.

"The IRIS study[1] and its companion long-term analyses[2,3] established the natural history of imatinib treated newly diagnosed chronic-phase (CP) CML. The trial cemented the importance of achieving an early complete cytogenetic response (CCR) and major molecular remission (MMR) — therapeutic milestones that translate into excellent long-term responses.

No patients who achieved an MMR by 18 months progressed to the accelerated or blast phase. With eight years of follow-up, 85 percent of patients remain alive, the estimated event-free survival is 81 percent, and freedom from progression to advanced CML is 92 percent.[3] Annual rates of progression to advanced CML remain less than 0.5 percent after five years.

Despite ushering in a revolution in the treatment of CML, these data indicate that imatinib leaves some people behind on the battlefield....." ***Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia: Passing the Baton*** *Jason Gotlib, MD, MS September 1, 2010*

The IRIS study showed that first line therapy with imatinib had a significant impact on patient survival. The study remains updated 8 years on.

Summary:

Pre 1997, **interferon alpha** (IFN) was used as first line therapy along with **stem cell transplant** in suitable patients, but the side effects of IFN were sometimes felt to be worse than the disease symptoms and very few patients showed a cytogenetic response.

Autologous transplants: patients Ph+ cells where separated from normal cells by a process called **Leukopheresis**, the normal cells are given back to the patient in order to delay disease progression by a few years.
Hydroxycarbamide (Hydroxyurea) is sometimes used *pre therapy* in order to help reduce dangerously high white cell counts. It has no impact on disease progression.
From 2003, targeted therapy has been used as first line therapy for CML in chronic phase, in some cases of accelerated phase and blast stage patients.
Since 2005, 2nd Generation TKIs have been available through clinical trials.

In 2012 dasatinib and nilotinib* were appraised as 1st line therapy in the UK by NICE.

*Nilotinib as priced with a PAS was approved as 1st line therapy, firstly in Scotland (SMC) then followed by NICE approval for use in the rest of UK.
Dasatnib, is equal in clinical effectiveness but is only available through the CDF (9 out of 10 cancer drug funds) in England, and through individual patient request schemes in Scotland, Wales and Northern Ireland.

11am: Dr Zor Maung, Western General Hospital, Edinburgh.

How do we measure response to Therapy?

In his historical overview, Dr Maung also mentioned 'Fowlers Solution' (Arsenic) as one example of treatment prior to the development of Interferon Alpha and bone marrow transplantation. He quickly moved on to the post IM era and showed a slide with the cover illustration of TIME magazine in 2000.

He explained how the excellent early data which was produced by the phase I and II trials of imatinib, then known as STI571, produced a rapid FDA approval of imatinib.

Again he mentioned the **IRIS Study** which showed the clear advantage of IM over IFN and Ara-C.

There was a high cross over rate from the non imatinib arms of the study - this affected the gathering of comparative data, but was a consequence of the success of this new therapy.

The 8 year follow up of the **IRIS study** shows that around 55% of patients enrolled are still treated with imatinib. Nevertheless, this study indicates an overall survival of 85% and if you discount non CML related deaths, this figure is even better at 93% OS (overall survival).

Annual rates of progression are low- a high of 2.8% in the first 2-3years of the study, after this the rate is very low.

This does leave **37%** without CCyR because of resistance or intolerance.

This is an unacceptably high percentage of patients so, **"what do we do?"**

- Optimisation of IM in 1st line therapy:
- Adherence is a big issue in the longer term.
- The main reason behind intentional non-adherence is due to side effects.
- Intolerance is a big problem and affects quality of life.
- It is remains a problem for some patients over the longer term.

There is a need to understand the real reasons behind why such a high percentage of the trial cohort stopped therapy, but he said at least 25% stopped because of unacceptable levels of side effects.

How can these results be improved upon?

SPIRIT 1: 636 patients were randomised to **4** different therapy arms.

A= IM 400mg; B= IM 600mg; C= IM + Ara C ; D= IM + IFN

From data collected at 4 years event free survival (EFS) is no different between the 4 cohorts of patients. Other trials have shown similar or the same results as **SPIRIT 1.**

The **German CML lV Study** and the

MD Anderson Cancer Centre study in the US.

Other International studies:

The **ENESTnd** (nilotinib vs IM) and **Dasision** (dasatinib vs IM) studies both show advantage over IM in the first line setting, although there is no significant difference in overall survival (OS).

* **Nilotinib** may be effective in preventing the development of resistant mutations if used as 1st line in chronic phase CML.

Early major cytogenetic response (MCyR) and major molecular (MR) responses are good in both trials with large numbers achieving fast complete cytogenetic response (CcyR).

Dr.Maung stressed that imatinib is still a good drug and effective for a majority of patients, so should not be ignored.

Side effects are the main issue with a significant minority of patients showing varying degrees of intolerance to imatinib.

In cases where side effects have a negative impact on quality of life (QOL) doctors should consider switching therapy to a 2G TKI. Patients need to tell their doctor if they suffer from side effects so the management of their treatment and disease achieves the best possible outcome.

Given that **intolerance** is a major reason behind a lack of adherence. This has a major impact on cytogenetic and molecular responses and patients should not hesitate to tell their doctor if side effects are causing on-going problems. If your treatment centre has a Clinical Nurse Specialist (CNS) or support nurse you might feel they can then help you tell your doctor if there is a problem. You should *not* suffer in silence.

The Yellow Card programme for reporting side effects is available but Prof. Clark thought it not very successful as it is such a time consuming system.

One audience member thought it might be a good idea to have a data collection system where patients could self-report side effects.

10.50am: Dr Jenny Byrne, University of Nottingham.

Second Generation TKIs: when should be use them?

The IRIS study shows IM is a good drug, but this only includes data from patients in clinical trials and out of an initial **553** patients enrolled on the IRIS study, only **332** continued on the study. That means that **221** discontinued for one reason or another.

What about how patients respond to therapy in the 'real world'?

Data from **224** patients treated at Hammersmith Hospital, show that although **62%** continue to do well on IM over time, **38%** that do not. Alternatives are needed.

- Resistance is the main reason for discontinuation, intolerance for the remainder.
- Side effects are the major cause of non-adherence over time**.**

In addition, in the 38% that does not do well on imatinib.

- Primary resistance
- Acquired resistance **–** usually within first 2-3 years of IM treatment some develop resistant mutations, this is termed 'acquired resistance'

Monitoring: goals as outlined in **ELNet 2009* guidelines** (NCCN in US) should be followed by all clinicians. * ELNet Guidelines will be updated in 2013

Target points for reaching HR; MCyR and CCyR should be used to monitor responses.

If **goals** are not reached within **ELNet target points**, a switch to 2G TKI should be offered.

2G TKIs in 2nd line

Dasatinib - active against most resistant mutations but **not T315i**.

In studies, **40%** IM resistant and **60%** intolerant patients achieved CCyR.

- Has side effects but they do not cross over from other TKIs
- Low platelet counts - need careful monitoring.
- **Pleural effusion** (a build-up of fluid on the lungs, heart or other tissues) potentially serious problem for a small number of patients, requires a break in therapy. If PE returns after resumption, a switch to different TKI essential.

Nilotinib : active against most resistant mutations, but **not T315i**.

Studies show deep MMR achievable.

- There are side effects but these do not cross over from other TKIs
- Rash is common -can be resolved with stopping therapy for a time
- Pancreatitis- rarely.
- Long QT Syndrome, nilotinib is not suitable for patients with this rare condition.

In both 1st and 2nd line nilotinib and dasatinib have advantage over imatinib. The kind of mutation identified will influence the choice of 2G drug.

Cancer Drug Funds and Individual Patient Requests

9 out of the 10 regional CDFs (England) have agreed to fund requests for dasatinib. In Scotland, Wales and Northern Ireland access applied for through Individual Patient Request Applications

New TKIs

***Bosutinib** (Bosulif, Pfizer) has shown good results in patients who do not respond optimally to other TKIs. It has an FDA and EMA licence applications and will undergo a NICE single technology appraisal for use after any other 1st line therapy in 2013.

Side effects are manageable and include:

- Transient gastrointestinal problems which are generally resolved in the first weeks/months.
- Nausea
- Musculoskeletal pain

Ponatinib (Iclusig, Ariad) specifically developed to treat **T315i** mutation and is effective in CP, AP and BP CML as well as Ph+ ALL .

Side effects include:

- Rash
- Pancreatitis in small group
- Phase 3 data from PACE trial is very encouraging in all scenarios.

The company is currently hopeful of a FDA fast track approval and if forthcoming will apply for EMA license in 2013.

Are 2G TKI more effective in 1st line? Clinical studies will answer this question.

SPIRIT 2 is still open and recruiting

ENESTnd data show nilotinib has high rates of CCyR and MMR over IM, with faster and deeper responses.

DASISION, data show dasatinib has similar results to nilotinib with improved response over IM.

Studies show 2G TKIs show superior responses over IM in 1st line use.

Summary:

- **2G TKIs** are effective in 2nd line,
- Side effects are and will remain an issue for some.
- TKIs preferable to SCT:
- **3G TKIs** are imminent
- **SPIRIT 3** – due to open in early 2013:
- **STOP/Discontinuation Studies** - planned

Q&A

Q: Are mutations during imatinib therapy caused by TKI therapy? How does resistance develop?
A: It is not likely that mutations are caused by TKi therapy, can be at low levels at diagnosis. As IM therapy reduces the numbers of Ph+ cells, those with mutations take over.

Q: Imatinib will become off patent soon, is there a danger that NICE will reassess.

A: There is a concern that generics might not be equivalent to imatinib. Novartis is the company that manufactures imatinib and is the biggest manufacturer of generics. it is more than likely that they will manufacture imatinib as a generic.**

****Prof. Clark stressed that the Indian generic is NOT an equivalent to imatinib.**

Q: Can Vitamin D be effective in CML?
A: Both Vitamins D and A have been studied since 1980s in mice-Vitamin A has shown efficacy in treating APL and Vitamin D shows some effect in lab mice but is not proven in CML and evidence is not there. However, vitamin supplementation can help keep us generally healthy.

Afternoon Session

2pm: Professor Stephen O'brien Newcastle University: 'Update on Clinical Trials'

SPIRIT 1: Phase III, RCT (randomised clinical trial) for newly diagnosed CML

The study opened for recruitment in June 2005 and recruited 256. Stopped recruiting in February 2009. All patients randomised in equal proportions to one of the following three treatment groups:

a) Imatinib monotherapy 400 mg daily
b) Imatinib monotherapy 800 mg daily
c) Imatinib 400 mg daily \+ 180 µg/wk pegylated interferon*

***Arm C closed because it failed to recruit patients.**

International Trials

France - did better with Arm C and found in favour of IM + IFN
Germany - not convinced that addition of IFN to IM provides any improvement.

Primary endpoint: compare overall survival (OS) in the three arms at 5 years

Secondary endpoint: MR (molecular response) at one year.

*Overall survival were no different between arms

SPIRIT 2: Compares imatinib 400mg with dasatinib 100mg once daily.

- Currently still open and recruiting newly diagnosed patients
- This is a popular trial in the UK.
- 770 of the 810 quota have been recruited at 172 sites, with 246 patients recruited last year.

Professor O'brien went on to show some 'Isotypes' (An International System of Typographic Picture Education, or 'picture language' developed by Otto Neurath) he had designed in order to show the difference in overall survival outcomes between IM and a 2G TKI - nilotinib.
His Isotypes showed that most patients will survive very well on imatinib and 'will be fine'.
He does not see a significant difference between TKIs for most people diagnosed in CP CML.

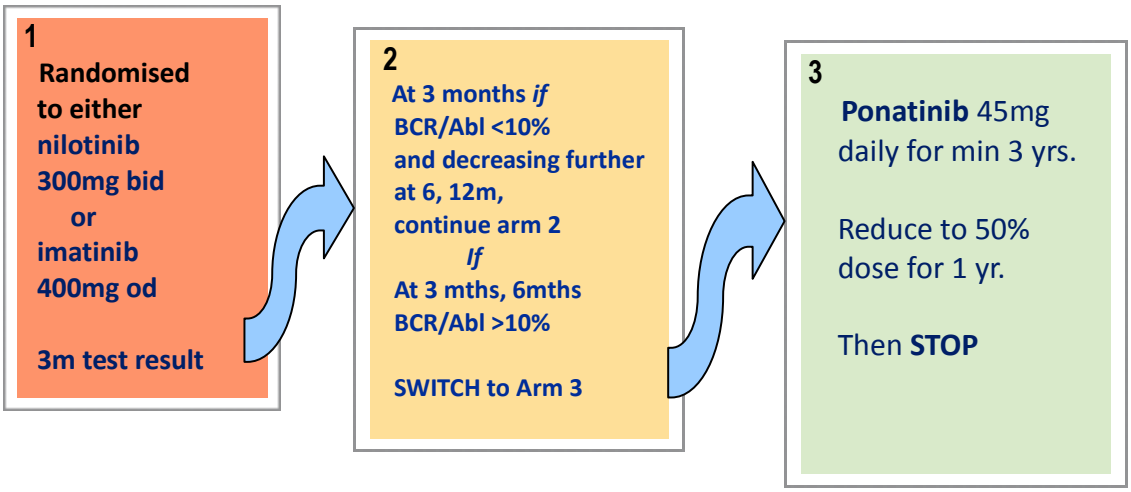
Prof. O'brien admitted that "new technologies are fantastic", but he said that cost to the NHS is an issue that cannot be ignored. He acknowledged that not everyone might entirely agree with this position.

He moved on to talk about stopping trials

- **French STIM study (STopIMatinib)**
- **DESTINY** – a UK study using dose de-escalation for those with sustained deep molecular responses of MR4 and lower.

Rather than replicate **STIM**, the **DESTINY** study will try to discover how to help a larger percentage of stable molecular responders to **stop** and maintain stable MR4 and lower without therapy.

SPIRIT 3: Newly Diagnosed Chronic Phase CML: 3 Scenarios

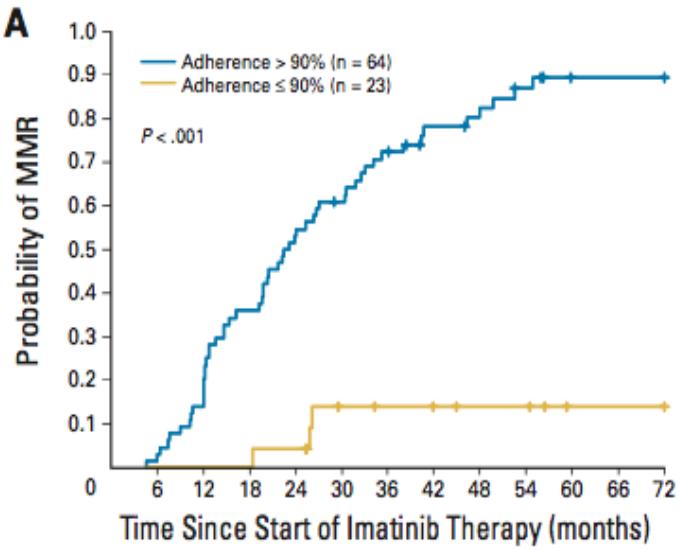


SPIRIT 3 will start recruitment in 2013.

3.20pm: Dr. Dragana Milojkvic, Consultant Haematologist, Imperial College London

Taking the tablets- why is it so important not to miss any?

Dr. Milojkovic took us through the issues surrounding lack of adherence amongst CML patients and showed slides of the MEMS Study conducted by Hammersmith. This used electronic containers as an independent measure of when patients did and when they did not take their therapy. This was combined and compared with self-reporting of non-adherence by the study patients. All patients were informed that the containers recorded when they were opened.



In a study of 87 patients for a period with a median of 59.7 months, showed that there was no molecular response (MR) if adherence to therapy was <80%, and no deep MMR (MR3 or more) if adherence was < 90%.

Research shows that MMR collates to progression free survival.

- In UK **26%** of CML patients are **less than 90%** adherent. Data from the **MEMS** study show only **40%** of the study participants were fully adherent to therapy.
- This surprised some participants as they had thought they were taking their therapy correctly
- Those that were fully or >90% adherent achieved faster and deeper molecular responses corresponding to greater than MR4 (4 log reductions).
- More than 3 doses missed in a month (less than (<) 90% of doses) will have an adverse effect on the level of molecular response.
- <80% adherence increases the risk of disease progression or development of resistance.

Microelectronic Monitoring System (MEMS 6 TrackCap)

Records the time container is opened
Most reliable method of measuring adherence to therapy.
Patients were not told about the chip

Marin D, et al. J Clin Oncol. 2010;28:2381-2388.

Full adherence to imatinib is critical for achieving molecular response

MMR = 0.1% (IS) > 90% adherence to imatinib therapy
MR4 > 90% adherence to imatinib therapy
MR4.5; MR5 > 90% adherence to imatinib therapy

Reasons for lack of adherence:

- **Internal factors:**

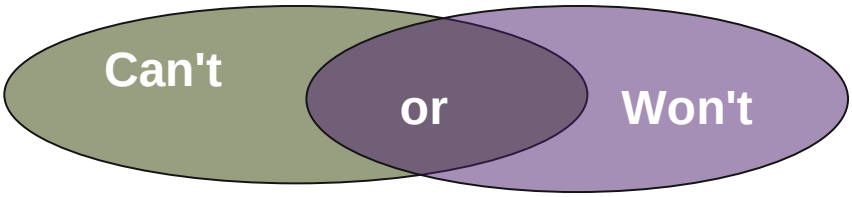
Memory; Beliefs about treatment; Beliefs about illness
Recall/understanding treatment instructions; Mood (depression, anxiety)

- **External factors**

Communication; Information; Cost; Culture; Social support; Media; Health policy;
Views of significant others

More than 200 different causes of non-adherence have been identified

Un-intentional non-adherence and **Intentional** non-adherence



Identifying Patients Non-adherent to TKI Therapy:

- Open and nonjudgmental communication
- Identification of suboptimal response
- Plasma drug levels
- Self-report measurements
- Electronic monitoring with/without feedback
- Assessing predictive factors

Practical Strategies to improve adherence to TKI Therapy

It should be recognised that:

- A significant proportion of patients fail to take their prescribed dose of imatinib- is that you?
- Adherence to therapy is critical for optimal response
- TKI therapy is very effective, if drugs are taken as prescribed

2.40pm: Dr. Farrukh Shah, University College London: ‘Taking the tablets. How can I make this easier?’

Dr.Shah’s specialty is Thalassemia Major which has a high factor of non-adherence. In her experience she has found that the only way to overcome patient's resistance to taking their therapy is by building more harmonious relationships between doctors and their patients.

She started by explaining that the word adherence might not be the right term– being 'forced' or 'required' to adhere. Patients feel a loss of autonomy.

Concordance or accordance is more likely to send the message that the patient is involved in their own treatment path and is equally responsible. The challenges underlying all treatment plans no matter what the condition are in most cases to do with the levels of side effects as well as an understanding of how a therapy or drug actually works.

What motivates good or full concordance/adherence?

Key relationships:

- Partners, close family/relatives, friends
- Doctors
- Nurses
- Psychologists

In any relationship, particularly the doctor/patient one there should be:
Mutual trust; honesty and freedom of expression.

Doctors and other health professionals should not judge and should try to understand the individual’s problems underlying their lack of adherence to therapy.
A social circumstance has an effect on an individual’s general attitude to life, feelings of defeat and/or failure can lead to a negative attitude about the future.

A good quality of life is essential if we are to build a positive attitude which in turn helps us value ourselves and regain a sense of control over our own destiny.
Understanding this goes a long way to help patients understand and manage their disease successfully.
Fear of outcomes and/or negative consequences need to be confronted and talked about if patients are not to be overwhelmed- caregivers, partners, close family members or someone who can take the time to listen can be of enormous help and directly affect how a patient deals with the need to take therapy every day for the long term.

Adherence to therapy is critical if you are to achieve a good outcome. If you cannot tell your doctor about worries and/or side effects and how your quality of life is affected, then tell someone else. If there is a support nurse at the clinic then they can often be of great support and help. It is the duty of doctors to find solutions, but they cannot do so if you do not communicate with them.

*Note: Patient forums like the **CMLS Group** discussion forum are an invaluable resource in this situation

3.40pm: Professor Richard Clark, University of Liverpool: 'Stopping Treatment- Who and When?'

Professor Clark started by explaining the meaning of MMR and CMR. There is a recent consensus amongst CML clinicians that the 'C' in CMR is unhelpful because this implies 'cure' which might be a source for confusion for patients. The term MMR is more accurate in describing what is actually achievable with current therapies.

Stopping Treatment

French STIM Study: 100 patients

Of 100 patients enrolled 39% remain in MR5 at 4 years

59% of trial patients showed signs of disease recurrence within most within first 6 months off therapy, a minority within 9 months. All patients who elected to restart IM therapy responded and achieved MMR at previous levels. 1 patient took a little longer to get back to previous level of molecular response.
Interestingly 5 patients refused to go back on therapy- some of these a still molecular positive but have not progressed to higher levels.

Can we predict those that will relapse?

There were more men than women that held their MMR- but we don't know why.
We know that the longer patients are in MR4.5/MR5 before stopping, the chance of holding response off therapy is improved significantly.

STIM trials in the UK?

Replication of STIM would be of little benefit to research and anyway the French are extending trials.

DESTINY

This study has been designed by the NCRN CML Sub-Group. It is a dose de-escalation study rather than a STOP study. The study will recruit 170 patients who have a stable low level of residual disease at MR4 or lower.

TKI dose will be halved:

- imatinib 200mg or 300mg- od
- nilotinib 200mg or 150mg- bid
- dasatinib 50mg- od
- monitored once per month by Q-PCR
- at 12 months- if RD remains stable at or below MR4- STOP
- Q-PCR monitoring until signs of disease recurrence

Professor Clark explained that funding and ethics approval are needed in order to set up the study. Ideally such studies are sponsored or 'badged' and currently it is proving difficult to attain this.
Funding:
DH were approached but did not approved funding.
Leukaemia and Lymphoma Research are considering funding, but have further questions about the study design. They are fairly positive but unlikely to reach a decision until March 2013.

Sponsorship

Can DESTINY go ahead without a NCRI badge? This is possible but will be at a reduced number of centres:

- Liverpool (trials unit might not approve)
- Hammersmith London
- Kings College London
- Leeds
- Newcastle (will go ahead without a badge)

Many patients who were present were very supportive of the de-escalation approach to stopping therapy and were rather frustrated that it was proving so difficult to find sponsorship or support, especially from the DH as studies and initiatives like DESTINY (and STIM) have to potential to save the NHS a lot of money.

As one member of **CML Support Group** commented,

> "....I found the whole story incredible especially when he told us he needed £200,000 to get the trial going, and, even if it failed it would save the NHS £2.3 million."

On behalf of CMLS Group Sandy said we are very willing to help support this study and offered to help in any way we can. We have been asked to hold off for a while until the situation becomes clearer.

Pregnancy

Patients with low MR who want to start a family can stop therapy with monitoring for the duration of the pregnancy. If still in MR after the birth they can continue 'off therapy' in order to breast feed, if desired, returning to therapy if and when levels of residual disease rise.

Conclusion

Professors Clark and O'brien thanked everyone for making the day so successful and invited those who did not have trains to catch to stay behind for an informal chat.
Unfortunately we did have a train to London to catch which left little time for catching up with members who I had not managed to talk with.

As ever time is always a problem at such meetings but I have managed to exchange emails with some of the delegates about how they felt the day's agenda met their expectations and needs. All were very positive about the clinical presentations and updates, but less so about some of the breakout sessions.

I was particularly disappointed with the session for caregivers as I thought the workshop lead had missed the point of the session by allowing patients to attend. Her preamble was centered more on patients with a cursory note to those who needed specific advice to talk to her colleague at the rear of the room. I left the session at that point but understand that after the initial slide presentation giving links to social media groups and standard professional patient information sites like Macmillan, Cancer Research UK etc. Attendees were invited to 'talk amongst themselves' whilst waiting for the opportunity to talk in private with the support nurse.

This session was an important opportunity to address the needs of 'carers'- needs that are undoubtedly 'unmet' – by providing a safe space to explore the feelings and emotions experienced by loved ones and family members when someone is diagnosed with a life threatening disease like CML, a diagnosis that affects everyone, not only the patient.

I was not alone in feeling that this session was a wasted opportunity. I strongly agree that it should be Carer led and closed entirely to patients.

CMLS group hope that we might be invited to advise on the agenda for next year's seminar and would be very happy to suggest individuals to chair or co-chair the very important Carer session.

Addition

Definitions and standardisation of RT Q-PCR

RT Q-PCR is a molecular test used to measure the levels of residual disease during therapy. It is expressed as a percentage of the ratio between the fusion gene BCR-ABL to that of a normal gene such as ABL (some labs use other genes such as BCR or GUS).

The Real Time *quantitative* Polymerase Chain Reaction or RT Q-PCR test is an essential tool that is used by oncologist/haematologists to measure response to therapy with Tyrosine Kinase Inhibitors (TKIs) in Ph+CML.

Initial testing with cytogenetics and FISH (in-situ fluorescence hybridization) are used at diagnosis and at the start of TKI therapy in order to assess early responses.

RT Q-PCR is then used to accurately detect reducing levels of BCR-ABL as the Ph+ cell population is reduced so significantly that they cannot be detected by normal cytogenetics or FISH testing. FISH and cytogenetics use blood samples taken from peripheral blood (FISH) or bone marrow aspirates and/or biopsy.

RT Q-PCR is used to monitor an individual's continued response to therapy and to detect BCR-ABL at levels that might indicate suboptimal responses, as well as indicating possible relapse and/or drug resistance. It can measure residual disease present in the marrow and can detect very low levels of Ph+ cells i.e. 1 Ph+ cell per 100,000 cells.

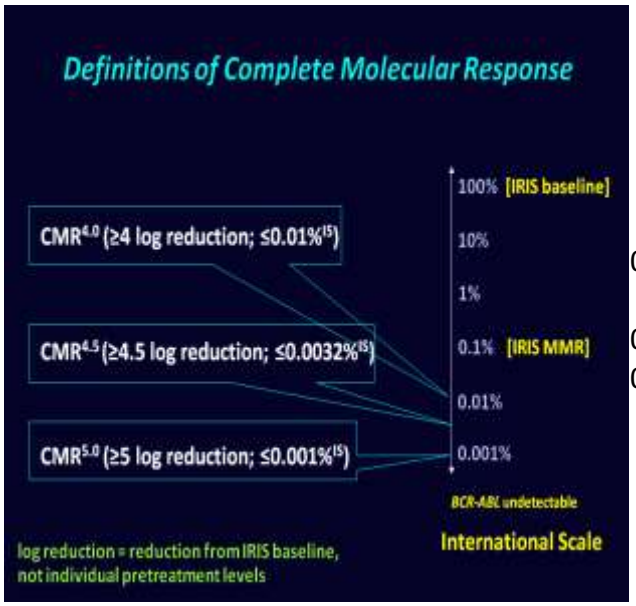
At diagnosis Ph positivity is 100% (IS)

As time on TKI therapy increases it is expected that patients will see a disappearance in Ph + cells in their peripheral blood- HR (haematologic response) within the first 4 weeks or so.
Thereafter there will be a major decrease of Ph+ cells produced in the marrow down to less than 10% by 3months continuing down to at least 1.5% (CCyR) within 6-12 months.

The target is at least MR3 (0.1% IS = 3 log reduction) or below within 12-18mths.

MR4 and MR4.5 is associated sustained response off treatment and may be the most practical current definition of CMR.

However, DNA PCR studies suggest that this does not represent complete eradication of disease



On the international scale (IS)
PCR test result of:

0.1% BCR-ABL = MR 3
0.01% BCR-ABL = MR 4
0.0032% BCR-ABL = MR 4.5
0.001% BCR-ABL = MR 5