A discussion of blood cancers and the MPN landmark survey

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Professor Claire Harrison speaks to Roshaine Wijayatunga, managing commissioning editor: Professor Claire Harrison became a consultant at Guy's and St Thomas' hospital in 2001. She is also deputy clinical director of cancer and hematology. She has influenced major advances in her field, including the description of key mutations and designing/leading global clinical trials, for example, the first JAK inhibitor trial in Europe. She is the chief investigator for several other international and national clinical trials.

She has strong international collaborations and authors many papers in peer-reviewed journals such as the *New England Journal of Medicine* and *Blood*. She has worked with enthusiastic patients to create a patient charity, MPN Voice. She is an internationally regarded expert in her field as a patient advocate.

First draft submitted: 4 October 2017; Published online: 21 December 2017

Keywords: BCR-ABL • hematology • MPNs • myeloproliferative neoplasms

How did you decide to pursue a career in cancer & hematology?

I think it was a love of basic science and the application of science to patient care, being at the cutting edge of both appealed to me. This was coupled with real experience of seeing clinical hematology as a medical student and junior doctor first hand.

How have you seen the field of hematology & hematologic oncology change during your career, & what are the main changes that you feel still need to happen?

There have been massive changes across the breadth of hematology as a discipline in the last 20 years – hematology being an incredibly broad discipline. For example, we have seen big changes in the field of hemophilia with the advent of new clotting factors, new treatment for hepatitis C and the hope of gene therapy and gene editing – which is much closer now!

At the same time, there have been similar advances in the field of thrombosis where understandings in science have been rapidly translated into patient care and I think that for me again underlines why I have such a great passion for this discipline.

At the other end of the spectrum is one of the most common inherited diseases – sickle cell disease – at the heart of hematology. We know about the genetic underlying basis of this condition and I think in the next 5–10 years, we will probably be carrying out targeted therapies to correct that underlying abnormality and considering therapies beyond, for example, things like bone marrow transplantation which are considered currently for very few sickle cell patients.

Thinking about oncology, I think hematology really has led the way in terms of understanding the pathogenesis of a disease and then delivering a targeted therapy. Great examples of this include *BCR-ABL*, being identified as an oncogene and then BCR-ABL tyrosine kinase inhibitors in chronic myeloid leukemia virtually leading to a cure for this disease and now we can talk about treatment-free remission for those patients.

On the other hand in the leukemia field, for example, we see the work of David Grimwade, Ellen Solomon and many others in identifying in promyelocytic leukemia, promyelocytic leukemia/RARA as a target to monitor and being able to deliver less intense therapies, so saving the lives of many thousands of patients by allowing us to understand what the concept of minimal residual disease is and that de-intensifying therapy for patients is possible.

As a chief investigator in many clinical trials, what are the main challenges that you have encountered with regard to clinical trial design in blood cancer?

It's often difficult to develop and take a medical therapy forward in terms of delivering it to the patient as quickly as we want to and that can be very difficult as a patient-focused clinician – to know that you have a patient in a Phase I/II clinical trial that looks promising and then to see a patient who is not eligible for that study because of a co-morbidity (such as a previous other cancer, for example, or slightly abnormal liver or renal function), and therefore not being able to deliver that therapy to that particular patient. This is more about academic and scientific rigor and bringing safe therapies forward, and as I have matured as an investigator, I have realized more and more that this is just how it is and unfortunately we have to deal with and discuss it with our patients.

I think also another issue is that sometimes clinical trials go too fast. For example, in our field, the biggest change which I have not mentioned so far is the description of *JAK2V617F*, a point mutation which is central to the pathogenesis of a rare group of hematological malignancies called myeloproliferative neoplasms, and the development then of drugs that target the downstream effects of that point mutation, mainly, kinase activation. We brought the first JAK1 and JAK2 inhibitor into the clinic 2 years after the description of the point mutation and what is really startling is how much quicker we can do that now. It was almost 40 years after the *BCR-ABL* oncogene was described that we managed to bring the inhibitors into the clinic. This is most likely down to advanced technology.

But the problem then is, we do this work, we just approve of an agent and then we try to bring forward alternative agents and sometimes, there are signals that might have been picked up in earlier-phase studies – had they been a bit bigger, had we been not quite so swift to initiate a Phase III study among others, and so it is balancing what is a pressing clinical need against the proper rigor in bringing forward therapies.

The other challenge for me is that we do not really have a good model of human disease, so we can use mouse models, we can use cell lines, but they never really replicate human disease and that is a huge struggle.

What inspired you to cocreate the patient charity MPN Voice & what does this charity stand for?

For me, it was actually my patients that inspired me. I became a consultant in a big hospital in central London and was seeing patients who really could not find any information about this condition myeloproliferative disorder at the time anywhere. The Internet was not nearly as powerful as it is now and if you, for example, Googled myeloproliferative disorder which was what myeloproliferative neoplasms were known as then, you could find multiple personality disorder but you could not find out anything about this hematological condition. This was a key driver for the creation of this charity [1].

The other thing was that I could see that the pace of advancement of science was quite great and I thought it quite likely that we might be able to identify better therapies and to test the genetics more rapidly which indeed we have. I therefore thought that there was a need not only for a patient community to support and inform patients, and to work with the medical and nursing community but also to advocate for patients in terms of getting the approvals for newer therapies more rapidly in the health economic environment.

How important is it in your opinion for clinicians & other oncology professionals to become involved in patient advocacy?

Every clinician does some degree of patient advocacy but in its widest sense I do not think it is a must for everybody. I do think it is a very rewarding thing to do and it is really important for patients to know that clinicians are passionate about their voice and their role in policy, for example, and health education. I believe, if you look at the medical community and you look at the roles that people play, everyone has a different role. I think it is incredibly rewarding from my perspective – I have actually learnt a lot about the disease from my patients – reaching them in that context, but as I said, I do not think it is for everybody.

What is the current standard of care for the rarer blood cancers such as myelofibrosis, polycythemia vera & essential thrombocythemia?

The current 'standard of care' depends on the health economy. Interestingly, I just ran a small education session for colleges from South America and what is 'standard of care' there is different from what 'standard of care' is here in the UK, and that will come as no surprise to the readers. Here, 'standard of care' is trying to achieve an accurate diagnosis and risk stratifying the patients. These three disorders are quite different (although there are similarities between polycythemia [PV] and essential thrombocythemia [ET]). When we are stratifying the patients we think about risk of thrombosis, risk of long-term late events and then we tend to treat those patients based on that risk stratification. Often we are using, for ET and PV, drugs just to lower the blood count and the most commonly used drug is probably hydroxyurea but there are questions regarding its efficacy and its long-term toxicity if being used by the patients for very long. Thus, there is always an anxiety that we may be storing up late effects for them, such as, for example, risk of leukemia, and striking recent data have shown significantly increased risk of leukemia for these patients, but because of the rarity of the conditions and the longevity of the patients, it is quite difficult to collect data because often the treatment spans for the patient goes beyond the career span of the clinician and the treatments change a lot throughout the course of the disease and patient's care.

There are other agents that we use, but really, we are only targeting reduction of thrombosis. We really need to take the next step and identify possible everyday life issues for these patients such as fatigue, and issues from their working life and home life. We are increasingly becoming aware of those, and the issues are highlighted in the Landmark Study – which will be touched on a little bit later on in the interview.

We are trying to bring forward therapies and test them in a better way for those patients. In terms of myelofibrosis – this is a much more aggressive disease and so 'standard of care' is effectively to consider a transplant, (95% of patients would not be eligible), and then it is about trying to treat the individual aspects of the disease. The JAK1, JAK2 inhibitor ruxolitinib has almost effectively become the 'standard of care' for intermediate- and high-risk patients with myelofibrosis. There is an open question about what should we do with low risk (sometimes also including early myelofibrosis), which specific method to use, what are not we including early on, what should that information be – we need to work toward trying to find these answers.

What were the main objectives of the MPN landmark survey?

The objectives of the MPN landmark survey [2] were to try to reach a large number of patients and clinicians in the different countries that were involved, including, Australia, Canada, Italy, Germany and the UK, and to try to address the burden of having disease. This burden of disease was effectively considered in terms of not only symptoms but also what the patient's perception was about the effects of the disease upon their home life, their work life. Conversely, we also aimed to tease out what the views of the clinicians was, and although we did not do a matched analysis between patients and clinicians, we did get clinicians' viewpoints. We also asked a little bit about what the patients felt about their healthcare support – did they discuss what they wanted to discuss with their clinician, how long did they have with their clinician, what more would they think they would want to discuss, were they aware of which group they sat in, among others. So it was quite a complicated survey and it was very revealing in terms of many of these aspects.

What were the main findings of the study in terms of symptom burden?

Actually the findings of the study very much confirmed what we had already seen previously but ratified it in such a very broad patient group. It was really very striking that the majority of these patients do have symptoms, these symptoms do have an impact on their personal life and if they were working while sick, many of them had taken a day sick in the last week to month as a result of their disease – that was a complete eye opener for me, as well as the fact that many patients, even those we thought we would regard as low risk or early disease were experiencing a significant symptom burden. Additionally, there was some other interesting insight in terms of what the aims should be for the clinician and aims of therapy for the patient and I think the patients were very much saying, *"I want a normal life and blood count, and I do want a good quality of life, but I actually want to focus on a cure."* The physicians were thinking more in terms of about what is available, for example, treating the risk of blood clots.

What did the investigators find out about symptom severity & the potential disconnect in patient & clinician perceptions?

We found that symptom severity could be quite great even for patients, as I said before, with early risk disease, so that was quite surprising for some, and actually the physicians in these countries were quite aware of the patient symptom burden in a previous Landmark Study that was performed in North America [3]. Just as a note, the original landmark study was the North-American one, the one that we are discussing in this interview is the international landmark study.

How important is it for patients to have adequate time to discuss their symptoms & symptom management with their clinician?

Of course, it is really important and I think it is a difficult discussion because in the medical environment, we are constrained by how much time we actually have to allocate to patients, particularly if they are often on the follow-up visit that is usually shorter than a new patient visit, for example.

Often these symptoms need careful dissection, for example, fatigue is very common in malignancies, but it also correlates with other issues such as depression, so it may well need the careful analysis by a team that is fairly used to doing this. In my hospital, we work very much with a team who assess affected patients in a holistic manner. I cannot emphasize enough how helpful that kind of intervention is, and we would then refer the patient on to other specialists such as a psychologist, dietician, physiotherapist and occupational therapist, sometimes singly, and sometimes in the context of what is known as a fatigue service.

What is the significance of this Landmark Study & what are the next steps?

In my opinion, the significance of the study is great. There were a large number of patients that were involved in the study, along with a large number of clinicians, and the impact of symptom burden was highlighted. We do quite a lot of work trying to understand what is underlying these symptoms and how we can best measure them, what happens to them, etc. We have got an ongoing study called the MEASURE study that is actually purely clinician led from a collaborative and is being run in collaboration with MPN Voice among other charities and we have collected data now from almost 500 patients in the UK alone, looking at what happens with standard therapies – something we really need to understand better [4].

I think Landmark also shows the power of the community and the collaboration with the clinicians and we should harness that. We should be addressing our treatment strategies beyond just the burden of symptoms – we should be addressing what the patients are actually wanting us to look at, a little bit more. This will also help us to move forward in terms of trying to make patients' lives a bit better, acknowledging that they do have symptoms and trying to put in place valuable medical therapies and paramedical – or more holistic therapies but also, actually then taking that information back to everyday lives. For example, determining how best the patient can function in the work place perhaps with flexible or reduced hours, among others. So I think there are many ways in which this survey can help and I look forward to doing more work on this in the future.

Disclaimer

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Financial & competing interests disclosure

C Harrison has received speakers fees and honoraria from Novartis, Shire, Celgene, Gilead and research funding from Novartis. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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