Update on the MDS Research Program at Sunnybrook

AAMAC has recently awarded additional funding to the MDS Research Program at Sunnybrook hospital. We spoke to Dr. Rena Buckstein, the Head of Hematology Clinical Trials at Sunnybrook to learn more about the project.

Can you give us an overview of the MDS Research Program?

I started the MDS-Can registry about 20 years ago, with the initial plan to document the epidemiology of MDS in Canada, because it didn't exist before. It evolved over time to evaluating how MDS impacts quality of life, for example. We started initially just at Sunnybrook. Once we worked out all the kinks about what elements are important and not important, we then started asking other sites across Canada to join the registry. It started with patient characteristics and quality of life, then with the guidance of a geriatrician from Princess Margaret hospital, Dr Shabbir Alibhai, we began considering the impact of patient related factors like frailty, disability and comorbidity on clinical outcomes, not just the disease characteristics including chromosomes, blasts, etc. We wanted to know more about how the soil (the patient as host), not just the seed (the disease), impacts patient outcomes. Until then, prognostic models for survival have relied only on disease characteristics, rather than patient characteristics including other health problems, level of fitness and resilience. Therefore, we added to the registry the measurement of several geriatric domains including frailty, disability, and then co-morbidity using validated instruments that are conducted yearly and followed the patients to see how they did. We were able to not only validate the importance of MDS characteristics for predicting survival but also were able to refine and improve on these prognostic models by incorporating patient-related characteristics, most importantly frailty. We are trying to spread the word internationally about how important the consideration of frailty and comorbidity is. And we are internationally recognized for this work.

We've progressively added more sites across Canada and are represented in most provinces: We currently have 16 sites that are part of our registry and others that are interested in joining. When a patient joins the registry, they must be within a year of their diagnosis, based on a bone marrow biopsy. At baseline, we ask them to fill out several quality-of-life questionnaires, one of which was developed specifically for MDS patients and validated with the assistance of the registry (called the QUALMS).

A research assistant will then measure how fast they walk 4 metres, time them standing up from a chair and sitting down unassisted 10 times, and we measure their grip strength. That's the physical performance testing. Then we evaluate their frailty using the Rockwood frailty scale and an MDS-CAN developed frailty scale. We have them fill out a disability scale. All these tests take just minutes.

Now, what we're working on today is finalizing the evaluation of quality of life (QOL) over time – what are the elements that predict for improvements or decrements in quality of life? Is it disease related: are they becoming transfusion dependent or independent; are they on certain medications; does their risk score matter? What is emerging over and over is the importance patient related factors play in predicting QOL score directions. So, patients that are frail or have a disability have inferior QOL scores over time, independent of their disease characteristics such as their hemoglobin or their transfusion dependence. We are emphasizing the importance of considering patient-related factors in the evaluation of quality of life in clinical trials since they may impact the QOL scores at a magnitude that exceeds the achievement of transfusion independence or an improvement in blood counts. This is yet another example of how the Canadian registry is contributing to the literature.

The next step in the journey of managing MDS patients is to come up with a nimbler and easier to use QOL instrument that will capture the symptom and function components that are most important to MDS patients. Currently, we use more generic instruments used in oncology that ask questions about symptoms that may be less relevant to MDS patients and less likely to be impacted by disease. Furthermore, many of these instruments are complicated and lengthy, leading to survey-fatigue. We are working to come up with a 10-element instrument that can be used in real life and clinical trials to understand the impact of our therapies. We hope to have AAMAC representation at a meeting we are convening in the fall with international MDS experts to help address this issue and finalize the questions we will ask. Once the tool is validated, we would seek FDA approval so that it can become the de-facto MDS symptom instrument deployed in clinical trials.

Another useful aspect of the MDS registry is the provision of data for pharmaco-economic modelling. The numerical rating of health states (e.g. transfusion dependent, anemic, on a specific treatment) by our patients using the EQ-5D instrument provides 'health-utilities; that can be used in decision analyses done by governmental agencies to determine if a new drug is cost- effective. Sometimes, the drug works, but it is prohibitively expensive for the taxpayer so cannot be approved by the ministry of health for funding, unless the price is reduced.

Finally, we are providing 'real world' analysis of drug effectiveness. Does luspatercept achieve a 38% response rate in patients who are dependent on transfusions? At what dose? How long do they remain on treatment? It is important to study this because, when patients go on clinical trials, they are the fittest of the fit and do not really resemble 'real-life'. People get excluded for a number of reasons: impaired kidney or liver function, poor functional status, to name a few, so we don't always replicate the results of clinical trials in the real world. By interrogating our registry, we can then see if our results match those found in the clinical trial. For example, a while ago we published an article in the British Journal of Hematology, looking at Ontario data which found that the survival rate for people on azacitadine was nowhere close to the result found in the clinical trial which led to the drug being approved in Canada. This is important data that the government needs for their

economic modelling and but also for us in terms of what we can counsel our patients. We can apply more real-world data and frailty scores in the information we give patients.

Are these new prognostic approaches in place across the country?

The inclusion of mutation testing in the revised prognostic score the IPSS-M is now standard of care. The inclusion of frailty information in prognoses is not uniformly occurring across Canada, but many physicians are considering it. By sounding the drum repeatedly, it will eventually catch on. We are hoping to prove that frailty also refines the prognosis of the IPSS-M. The inclusion of geriatric testing is catching on in blood cancers slowly but surely.

Your project brief mentions digital twinning artificial intelligence analysis. What is that?

There are initiatives that recognize that the bigger the data set, the more you can do with it. When databases around the world can share their data together in an anonymized fashion, you can do more powerful modelling using artificial intelligence. We have submitted content of the MDS Registry to a partner in Italy who is doing this project. The Italian researcher has refined the prognostic and predictive models using digital twinning.

Anything else you wish to share about your research program?

Yes! We are piloting the OURA smart ring in a 12-week study in 60 patients with MDS, 30 who are dependent on red blood cell transfusions and 30 who are not. The OURA ring is a convenient 'wearable' that measures a patient's biometrics continuously. Patients can wear it 24/7 through all activities. I'm interested to see if the biometrics of someone with MDS has prognostic information (ex. inactivity, heart rate variability, sleep quality, etc.). I also want to compare the biometrics of those that are transfusion dependent with those that are independent, those that are severely anemic with those that are not, those that are fatigued with those that are not. How does sleep impact daily function? Our pilot study is enrolling patients at Sunnybrook. If it looks promising, I hope to get funding to deploy it across the country in more patients. It's objective, not subjective, like QOL questionnaires. We still have 21 more slots, so I'm happy to have patients be referred to this study.