WhiMSICAL Study Research Protocol

Scientific Title

WhiMSICAL (*Waldenstrom's Macroglobulinemia Study Involving CArt-wheeL: Empowering Waldenstrom's Macroglobulinemia patients to contribute patient-derived data for observational research (LNR/16/CRGH/30 – CH62/6/2016-025)*

Simplified Title

WhiMSICAL Study

Investigators

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Aim

To develop a continuously expanding data set to provide a platform for addressing hypotheses based around Waldenstrom's Macroglobulinemia (WM) patient-derived data, and also to:

- define the constellation of presentations and patient reported outcomes (PROs) of WM patients
- map clinical and pathology correlations
- identify real-world treatment and response data and disparities internationally

Hypothesis

The Australian and international WM patient communities are well versed in their condition, have a strong network, and are willing to participate in clinical research to further the understanding of their rare cancer. This wealth of patient-derived information will complement the less abundant, higher-level evidence of clinical trials and registry data.

Background

Waldenström's Macroglobulinaemia (WM) is a low grade Non-Hodgkin's Lymphoma, with an incidence of approximately 3/million people/year,[1-2] classifying it as a rare cancer (< 6/100000/year).[3] Rare cancers, by definition, are difficult to study in large clinical trials, resulting in a paucity of well-founded evidence. As such, the diverse manifestations of disease and response to different treatments are less understood compared to more common cancers.

WM is defined as lymphoplasmacytic lymphoma infiltration of bone marrow with a circulating monoclonal IgM paraprotein. These two features can often be asymptomatic and found incidentally, however there are a wide variety of symptoms that have been attributed to WM.[4] Identification of these symptoms is not always straightforward, particularly as they can non-specific, (e.g. headache, fatigue, epistaxis etc.). Disease-related symptom development is one of the major indications for WM treatment.[4] It is evident that a good understanding of WM and its symptomatology is necessary for evaluation and treatment of this patient population. Capturing as much patient data as possible detailing the constellation of symptoms WM patients experience would be of great value. In rare cancers, capturing plentiful data detailing the constellation of symptoms can be significantly limited in clinician-derived cancer registries and clinical trials. As a

result, patient-derived data is becoming an attractive option in gaining more knowledge of these diseases.

Unlike many other rare cancers, the WM landscape has fortunately had many new developments in treatment options. Several novel therapeutic agents have demonstrated efficacy, including rituximab and other monoclonal antibodies targeting the CD20-antigen expressed on the malignant cells, bendamustine, ibrutinib and other Bruton tyrosine kinase inhibitors.[5-8] These treatments however, carry a large financial burden and while some are Therapeutic Goods Association (TGA) approved, few are PBS listed for use in WM either in first or subsequent lines of therapy. Clinical trials data does not reflect real-world dilemmas such as funding and availability, resulting in a disparity between the well evidenced treatment and what is available. Patient-derived data allows for a global picture of different treatments geographically, including how they are accessed and the disease and symptom response.

Including patients directly in research through patient-derived data is a form of patient empowerment. Health care delivery in the current era has an increasing focus on patient centered care and consumer engagement as endorsed by many medical Colleges (the Royal Australasian College of Physicians, and equivalents in the UK and US), There are multiple examples describing how patient empowerment utilising this methodology has led to advances in different fields, such as psoriatic arthritis and aortic surgery.[9,10] Empowering the WM community has great potential to yield advances in knowledge of this rare disease.

CART-WHEEL.org (Centre for Analysis of Rare Tumors) is a global, online rare cancer database for patient-derived data. It is managed by Biogrid Australia, a web-based, real-time, data-sharing platform for collaborative, translational medical research linking de-identified, ethically-approved data across institutions and jurisdictions. Data is obtained through a carefully formulated questionnaire, with a correlative study demonstrating ~80% concordance with physician-entered data.

The international WM patient community has had extraordinary success in providing information and support. Led by the International Waldenstrom's Macroglobulinemia Foundation (IWMF), with Australian affiliate WMozzies, they provide information, education, peer support and promote WM research for affected patients and their families. Focused on a two-fold goal of support for patients/carers and advancing the search for a cure, they have achieved considerable engagement of a high proportion of WM patients globally. This is helped by the characteristic patient demographic for this rare tumour: patients are usually diagnosed aged in their seventh decade, often incidentally in an asymptomatic state, and given the slow progression of this disease, in the current era of internet connectivity, they have sufficient time to obtain significant knowledge about WM. The presence of readily understood haematology (Haemoglobin) and immunology (Immunoglobulin M) markers of their disease facilitates self-tracking of disease progression. The group leader of WMozzies (AW) and a board member of the IWMF (PdN) are investigators on this project. Both consumer investigators are endorsed by the IWMF as capable and informed stakeholders, able to represent the research priorities of the WM patient population.

Research Plan

Study Type Observational Study

Setting/Location Web-based platform with data analysis at CRGH

Duration of Study 5 years, then review

Methods:

Study Population	All ages
Recruitment	Continuous participant recruitment will be promoted through WMozzies, the Australian affiliate of the IWMF, Leukaemia Foundation Australia, and members of the Haematology Society of Australia and New Zealand. International promotion will be undertaken upon demonstration of feasibility locally, through invitation for promotion by the IWMFand other international haematology and WM communities including WMUK, Hematon etc. These relationships have been initiated and will be developed through involvement in International conferences and inclusion of International investigators in the future. Clinicians (haematologists and oncologists) within Australia and New Zealand, the European Consortium of Waldenstrom's Macroglobulinemia and those listed on the IMWF Physicians directory will be given information regarding the project and provided with a patient information pamphlet to give their WM patients. Patients will not provide written consent specifically for this project but will be able to register online to CART-WHEEL.org. Haematologists and departmental research staff will assist patients requiring information about treatment dates, medicine and doses, along with IgM and haemoglobin results. Some persons will have consented to CART-WHEEL without having heard directly about this research project. Upon ethics approval, the investigators will request access to data from all CART-WHEEL patients with a nominated diagnosis of WM and receive de-identified data without any patient having to specifically consent to this study. (Provided Ethics approval is noted by BioGrid as usual). *To further assist with recruitment, a study newsletter will be distributed every 3-6 months to the community groups as feedback to consumers*

	as to the progress of the study and areas for improvement in data entry for participants.
Number of patients	Aim of 1000 internationally
Key Inclusion Criteria	All CART-WHEEL.org questionnaire participants who have entered Waldenstrom's Macroglobulinemia or Lymphoplasmacytic lymphoma (LPL) as their diagnosis, with consent form received by BioGrid Australia, will be included.
Key Exclusion Criteria	CART-WHEEL.org participants with non-WM/LPL diagnoses
Study Treatment/Intervention	A WM-specific extension to the CART-WHEEL.org questionnaire was developed by the clinician and patient investigators, including questions on type/result and timing of: o Symptoms o Pathology: IgM, Haemoglobin, neutrophils, platelets, bone marrow involvement o Treatment access o Hospitalisation o Transfusions and plasma exchange *Future additions to the CART-WHEEL.org questionnaire will include a graphing function of Haemoglobin and IgM results in the patient summary provided at the end of the questionnaire, Euro QoL EQ-5D-5L questions and/or FACT-An QoL questions. The graphing function in particular is being developed in response to a request from the IWMF and WMozzies to improve the interpretation of results and provide participants with improved data feedback*
Control Group	N/A
Follow-up	5 years
Endpoints/Outcome Measurements Primary endpoints Secondary endpoints Confounders	The Primary Endpoint of the study is the number of data contributing participants recruited, demonstrating feasibility of a patient-derived registry and platform for testing hypotheses in WM. Secondary Endpoints that will be measured are: 1. Patient age and geographical distribution 2. Symptoms at Presentation 3. Symptoms at first treatment 4. Correlation between symptoms and pathology results

	5. Time to treatment from diagnosis 6. Treatments used, including doses and discontinuation, also including Red cell, platelet and intravenous immunoglobulin transfusion 7. Treatment adverse effects 8. Patient reported health status (PROs) 9. Treatment access (e.g. clinical trial, governement funded, special access schemes, self-funded, etc) and correlation to geographical location Potential confounders include limitation to higher educated, English-speaking, patients, with recall and attribution bias. Directed, simply-worded questions aim to address these, as well as patient education and feedback via IWMF correspondence, and the availability of direct patient-investigator participant support.
Statistical Considerations/Data analysis	Interim data analysis will occur approximately every 6 months after commencing recruitment in June 2016, with an anticipated 100 Australia (aim n= 85) and New Zealand (aim n=15) patients recruited by the end of 2017, followed by international promotion to recruit a total of 1000 participants. This will enable refining of the desired sample size based on identifying patient demographics and the likely feasibility of providing an accurate national and international snapshot of patient-derived experiential data. In the event that fewer than anticipated patient entries are received within the first 6 months, measures to increase participation will be considered. To address the confounders associated with patient-derived retrospective (followed by prospective) data, upon recruitment of 50-100 participants from clinician-derived registries, a validation study (with separate ethical approval) will be undertaken comparing this study's data to the registry data. Patients are encouraged to download and print a summary sheet of their own entered data which can be presented to their treating clinician as a data cleaning exercise. Categorical variables will be summarised in tables displaying frequencies of each category and

	represented as percentages of affected patients in the cohort. Differences in relevant factors, e.g. time to treat, treatment modalities, and changes in IgM levels, will be analysed across populations e.g. rural vs. regional, Country A vs. Country B, or Country A vs. global, using an independent samples t-test. Differences in response will be analysed using cross tabulation and Pearson Chi squared (P = 0.05).
Ethical Considerations	All data accessed will be de-identified and will be followed using the CART-WHEEL ID number and a designated study number. No direct patient contact will be made for clarification of information and no extra patient clinical investigations or interventions will take place as a result of this study. Patients complete a consent form and send it to BioGrid Australia prior to data entry to CART-WHEEL.org. The Principal Investigators of this study will have access only to de-identified data (participants are followed by a CART-WHEEL ID and study ID). Patients will not be consented specifically for this study. *Push-button online consent has been approved and will soon be available to CART-WHEEL participants to enhance international recruitment.*
Safety Considerations	As no interventions will take place as a result of this study, there will be no adverse reporting required. Confidentiality of participants will be preserved through the use of de-identified data and careful storage of collected data (see below).
Investigator obligations	All data will be electronic and be stored on password protected laptops utilised by the Principal investigators and backed up onto external storage devices which are also password protected in locked facilities. Following the study, data on laptops will be permanently erased and external storage devices containing study data will be physically destroyed (following storage for up to 15 years).
Funding	External funding will be from Janssen-Cilag P/L directly to BioGrid for application, data development, testing and associated costs. Internal Funding (Concord Haematology) will be provided as required in case of any shortfall

Conflict of Interest	Nil

Outcomes and Significance

The goals are that the gathered information will expand clinician's knowledge on the range of presentations, treatments, treatment responses and toxicities, along with patient reported outcomes using validated research tools, which will assist them in treating the participants. Information on treatment disparities, coupled with information regarding treatment efficacy may strengthen the clinical evidence for obtaining subsidised novel therapies sooner for patients. The establishment of a large patient-derived registry of WM patients can also facilitate improved recruitment in clinical trials to improve sample size, as participants can consent to being contacted for separate clinical trials.

References

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