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Article Title: WhiMSICAL: a global Waldenström's Macroglobulinemia patient-derived data registry capturing treatment and quality of life outcomes

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To the editor:

Waldenström's Macroglobulinemia (WM) is a low-grade non-Hodgkin's lymphoma with an incidence of approximately three per million-persons per year,[1] classifying it as a rare cancer. Rare cancers are inherently difficult to study in large clinical trials, resulting in paucity of well-founded evidence. As such, the diverse manifestations of disease and response to different treatments, including quality of life (QoL) outcomes, are less well-understood than in more common cancers. Patient-derived data can facilitate generation of large datasets to help address this gap.

A small number of treatment regimens for WM are identified as options for first and subsequent lines of therapy in international guidelines,[2] however, real-world treatment practices vary significantly.[3] This disconnect between clinical guidelines and real-world treatment availability and practice likely contributes to the global disparity in cancer survival.[4] Illuminating the nature of this disparity through global databases will assist in identifying areas in which to focus resource allocation. Patient-derived data can enhance the understanding of global treatment practices, as well as provide a complementary view of how treatments are accessed, their impact on QoL and other patient-reported outcomes (PROs). A systematic review of randomized controlled trials in cancer identified PROs as independently prognostic of overall survival,[5] thus, improved capture of PROs and QoL data in clinical care and research are essential.

Here, we present WhiMSICAL (Waldenström's Macroglobulinemia Study Involving CART-WHEEL), the first global database capturing WM patient-derived demographic, clinical and PRO data, and the insights gained from the contributions of 453 WM patients. Developed by WM clinicians and International Waldenström's Macroglobulinemia Foundation (IWMF) patient-investigators, WhiMSICAL aims to address patient priorities in WM research and map QoL and PRO data with treatment to help guide patients and their clinicians.

Recruitment began in June 2016, through patient-initiated registration at www.cart-wheel.org, (Centre for Analysis of Rare Tumors), an online rare cancer database hosted on the secure BioGrid Australia platform, for patient-derived data utilizing a comprehensive questionnaire. The www.cart-wheel.org study was approved by the Melbourne Health Human Research Ethics Committee (HREC 2007.260). The WhiMSICAL amendment to the www.cart-wheel.org online questionnaire capturing additional data points for WM was approved by the Sydney Local Health District – Concord Repatriation General Hospital Human Research Ethics Committee (LNR/16/CRGH/30). Patients complete a consent form online following registration and can provide multiple levels of consent (see supplement).

A total of 453 WM patients were recruited by the data analysis cut-off, July 2020, driven by social media messaging by the IWMF to members globally. Data completion rates were variable, with over 80% entering data for diagnosis, symptoms, treatment and PROs, reducing to less than 50% for pathology results. Patient characteristics are outlined in table S1. The population included participants from 19 countries, predominantly from the USA (46%) and Australia (26%). The majority of patients were male (61%), with median age 70 (range 27-88) years and the median follow-up was 68 months (IQR 34-117). Patients from the USA were compared to Rest-of-World (ROW) patients and were marginally older, but otherwise no significant differences were observed. Participants entered data on disease-related symptoms, providing date of symptom onset and end, as well as date of pathology results. The results were matched to the documented date of diagnosis. Fatigue/muscle weakness (46%), B-symptoms (21%) and peripheral neuropathy (19%) were the symptoms most frequently reported, with 30% asymptomatic at diagnosis. Interestingly, 10% of participants reported leg cramps at diagnosis. While close to half of the participants were anemic (Hb < 11.5g/dL) at diagnosis, few had other cytopenias.

Analysis of the data entered by 302 participants who had received treatment identified 46 unique first-line therapies after combining all clinical trial treatments (Figure 1A). This variation was maintained across countries, although higher in the USA with 36 unique therapies used (n=136) and 27 in the ROW population (n=166). The variation in therapies remained when considering first treatments initiated since 2016 (time of release of the last international guidelines[2]), with 19 unique therapies reported (n=125). Bendamustine and rituximab (BR) was the most common first-line therapy, 74/302 (25%) overall, and 55/125 (44%) of all participants treated since 2016.

Evaluation of global differences in treatment practice demonstrated that USA participants commenced therapy significantly earlier, with median time to first treatment from diagnosis being 48 days (IQR 15-265, n=116) compared to ROW median 100 days (IQR 17-755, n=131, p=0.04, Figure 1B), despite a higher proportion of patients with smoldering WM (USA 19%, ROW 13.7%). When comparing only those with active WM at diagnosis, USA patients began treatment at median 34 days, whereas ROW patients began at median 56 days (p=0.04). ROW patients were more anemic at first treatment, with median hemoglobin 9.8 g/dL (IQR 8.6-11.0, n=72) compared to USA patients; median 11 g/dL (IQR 9.5-12.4, n=57, p=0.006, Figure 1C). IgM levels were not significantly different at first treatment (p=0.60). Participants from the USA had 29% of therapies government-funded and 5% provided on clinical trials, compared to ROW, which had 57% and 13%, respectively (p<0.0001 and p=0.0008, respectively). Employer-purchased insurance was the main source of funding in the USA (43% of treatments, Table S2).

To evaluate treatment outcomes, time to next treatment (TTNT) was assessed for the four most common first-line therapies. Analysis of unmatched populations demonstrated encouraging TTNT outcomes in the first-line BR cohort (Figure 1D).

Patient-reported outcomes were measured using two tools: Impact of Event Scale-6 (IES-6),[6] a measure of current post-traumatic stress symptoms related to a cancer diagnosis, and the EORTC QLQ-C30 questionnaire. Based on IES-6 scores (ranging from 0=no stress to 24=maximal stress), at median 43 months (IQR 15-98) post-diagnosis, 10% of participants had scores $\geq$13, consistent with post-traumatic stress disorder (94% positive predictive value, Figure S1A). However, participants reported improvement in stress scores over time when comparing their first and last stress score entries (separated by a median 20 months, IQR 13-35, p=0.001, n=157, Figure S1B). Using the EORTC QLQ-C30 global scale in a snapshot analysis, patients taking BTKi had higher QoL scores, with mean global scale of 80.1±16.2 (n=44), compared to those not exposed to BTKi who had been treated within 12 months: mean 68.3±22.6 (n=57, p=0.004, Figure S1C). This was despite the BTKi cohort having undergone a median of two prior lines of treatment (IQR 1-4) compared to the non-BTKi cohort (median 1, IQR 1-2, p<0.0001).

These findings represent the largest reported patient-derived data source for a rare malignancy. WhiMSICAL is the first global WM registry for capturing clinical and QoL information, helping to bridge the gap in availability of data between this rare lymphoid malignancy and more common entities. Furthermore, it is agile, able to rapidly address current clinical questions, such as currently evaluating the impact of COVID-19 with additional questions to the registry approved and implemented within 14 days. This has been feasible only with the partnership of the patient community, involved not only as the sources of data entry, but as key investigators.

WhiMSICAL has identified marked global variation in WM treatment, persisting despite comprehensive treatment guidelines being released in 2016.[2] This highlights the fact that while guidelines exist, there may be lack of familiarity with, or access to, recommended therapies. USA patients are treated significantly earlier than their international counterparts, with ROW patients becoming more anemic before treatment is initiated. This may reflect geographical disparities in

access to certain therapies. WhiMSICAL offers a platform for a deeper analysis of the adoption and financial toxicity of WM treatments globally.

WhiMSICAL also generates outcome data in the form of TTNT. While the current analysis lacks comprehensive matching of baseline characteristics, many real-world insights are to be gained as the cohorts grow with longer follow-up. With ongoing parallel capture of PROs, the registry has the potential to continually map outcome and PRO data to treatments, aiding clinician and patient decision making.

Direct patient reporting in this study has allowed for greater understanding of their experiences and PROs. New insights include the high proportion of patients with leg cramps at diagnosis, and that 10% of participants have stress levels consistent with post-traumatic stress disorder. We demonstrate that despite a higher treatment burden, patients who are currently on BTKi have better QoL scores compared to those who have never been exposed to BTKi and have been treated within 12 months. With further data entry over time, these results can be confirmed with longitudinal analyses.

There are, of course, several limitations with a study of this kind, such as gaps in data completion and survivor bias. As international uptake of the WhiMSICAL database increases with time, it is anticipated that data entry will become more prospective and comprehensive, overcoming many of these limitations.

In conclusion, the WhiMSICAL study demonstrates feasibility and agility of an ethically-approved patient-derived data platform to provide direct insights of patients, including WM-related stress responses and how the diversity of therapies correlates with outcomes and QoL. Such real-world

PRO insights are rarely available in routine clinical practice but are increasingly important in the era of novel therapies.

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Authorship Contributions

I.T, A.W, E.M, P.L.D, J.H, M.B, D.K, C.H, C.L.S and J.T were responsible for study design. I.T and J.T were primarily responsible for data analysis, first draft writing and manuscript finalization. All authors contributed to data collection, data interpretation, carefully reviewed the manuscript and approved the final version.

Disclosure of Conflicts of interest

I.T and J.T received indirect research funding (to BioGrid Australia) for the initial www.cart-wheel.org database WM-specific amendment from Janssen-Cilag. JT reports institutional funding for trials from

Pharmacyclics, Beigene, Roche, BMS, Takeda, Janssen-Cilag and Celgene. A.W reports personal fees (event photoshoot) from Janssen-Cilag, outside the submitted work. S.O reports consultancy, honoraria, membership on advisory board and research funding from Roche, AbbVie, Janssen-Cilag, Merck, and AstraZeneca; consultancy, membership on advisory board and research funding from BeiGene and Gilead; consultancy, honoraria, membership on advisory board from CSL Behring; research funding from Epizyme, all outside the submitted work. S.D reports honoraria and research funding from BeiGene and Janssen-Cilag; honoraria from Sanofi, all outside the submitted work. M.K reports personal fees (travel grant and honoraria for advisory board) from Takeda, Roche (including for presentation), BMS, MSD, Janssen/Cilag, Amgen, Novartis (including for presentation), Kite/Gilead (including for presentation), Celgene and Miltenyi Biotech; research grants to institution from Takeda and Roche, all outside the submitted work. M.L.P received speaker fees from Pharmacyclics, outside the submitted work. A.J.O reports research grants to institution from Genentech/Roche, TG Therapeutics, Spectrum Pharmaceuticals and Adaptive Biotechnologies, all outside the submitted work. C.H reports stock ownership from AbbVie, BeiGene, Bristol-Myers Squibb, Gilead, Idera Pharmaceuticals and Calithera Biosciences, outside the submitted work. C.L.S is a Director of BioGrid Australia, the umbrella organization hosting CART-WHEEL.org. E.M, P.L.D, J.H, M.B, and R.L.S declare no competing interests.

Role of the funding source

Janssen-Cilag provided an initial research grant to a third party to fund the initial www.cart-wheel.org database WM-specific amendment. They had no role in designing the WM-specific amendment or any other aspect of study design; no role in data collection, analysis, or interpretation, manuscript writing, or in the decision regarding submission for publication.

Data availability statement

Original, de-identified data can be shared upon institutional review board approval by Sydney Local Health District – Concord Repatriation General Hospital Human Research Ethics Committee, and Melbourne Health Human Research Ethics Committee. The data are not publicly available due to privacy or ethical restrictions. For access to original data, please contact the corresponding author by emailing ibrahim.tohidiesfahani@health.nsw.gov.au.

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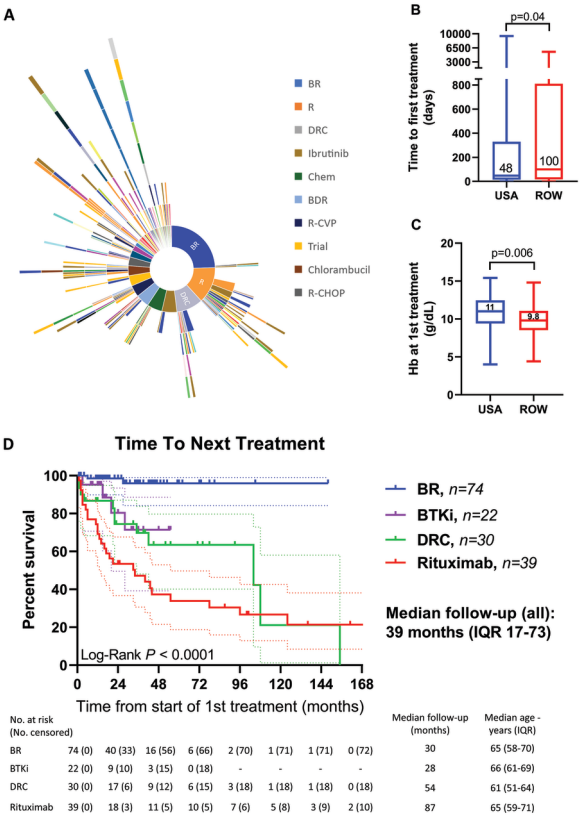
Figure legend

Figure 1. Global treatment practices and outcomes of first-line treatment regimens. (A) Sunburst chart displaying therapeutic regimens. Each color represents a unique regimen. The inner ring displays the first line of therapy, the second-most inner ring displays the second line of therapy for the participants with the adjacent first-line therapy and so on. The legend displays the ten most common first-line therapies. Clinical trial regimens that matched other listed regimens were included in the specific regimen, rather than under "Trial". (B) Box and whisker plot (range) comparing time to first treatment in days from date of diagnosis between USA participants (n=116) and Rest-of-World (ROW, n=131). (C) Box and whisker plot (range) for hemoglobin (Hb) at first treatment for USA (n=57) and ROW (n=72) patients. (D) Kaplan-Meier survival curves showing time to next treatment from the start of four different regimens used in the first-line setting: bendamustine rituximab (BR, n=74), rituximab monotherapy (n=39), dexamethasone rituximab cyclophosphamide (DRC, n=30) and Bruton tyrosine kinase inhibitors (BTKi, n=22). Patients who did not enter a subsequent treatment were censored on the date they last edited their data. R – rituximab, Chem – chemotherapy unspecified, BDR – bortezomib dexamethasone rituximab, R-CVP – rituximab cyclophosphamide vincristine prednisone, Trial – clinical trial, R-CHOP – rituximab cyclophosphamide doxorubicin vincristine prednisone, IQR – interquartile range.



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