Pathways of patients with chronic haematological malignancies: a report from the UK's population-based HMRN

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Scientific summary

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Scientific summary

Background

Population-based data are required to inform aetiological hypotheses, plan healthcare services and monitor the impact of therapeutic change in the general patient population. This need for data is particularly pertinent in fast-moving areas such as haemato-oncology, where treatments change rapidly and 'gold-standard' randomised controlled trials are absent or restricted to specific subgroups (often younger patients with fewer comorbidities), to specific time points (commonly first-line treatment) or by factors such as socioeconomic status, gender or ethnicity.

Arising in blood and lymph-forming tissues, haematological malignancies (leukaemias, lymphomas and myelomas) are, collectively, the fifth most common cancer. With diverse aetiologies, treatments and outcomes, more than 100 subtypes are currently recognised by the World Health Organization. Although the incidence of these cancers is stable in high-income countries such as the UK, prevalence is increasing due to population ageing and the development of new multifaceted regimens (e.g. chemotherapies, radiotherapy, stem cell transplants, novel targeted agents). However, around 60% of blood cancers remain incurable, with management often beginning with regular hospital-based monitoring, known as 'watch & wait' (W&W). While some patients may never need treatment, others often experience a remitting–relapsing care pathway, requiring treatment at progression interspersed with further monitoring. As with many chronic conditions, there are often uncertainties regarding how individual trajectories will progress, and variations are evident in the need for (and response to) treatment; the most effective regimen; the time when treatment is required (if ever); and the impact of treatment (and non-treatment) on quality of life.

Despite such complex trajectories, many of which are associated with anxiety-provoking W&W, and therapies that impede quality of life and incur marked healthcare costs, empirically-based incidence and prevalence estimates relating to treatment states (W&W, first-line treatment, second-line treatment, etc.) are lacking, and granular population-based evidence to guide treatment decisions is sparse. Importantly, new data-gathering measures to redress this deficit have been introduced in the UK but are presently insufficiently mature to guide decisions, and the rapidly evolving nature of haemato-oncology means that generic sources may never be adequate for assessing particular therapies and their impact on individuals. Furthermore, most health economic models have been developed to reflect specific (often static) decision problems, despite effective clinical management being dynamic, involving treatment, monitoring and therapy switching, and depending on treatment response and disease evolution.

To summarise, there is a dearth of accessible, reliable information to guide clinicians and patients about treatment and associated healthcare activities, physical health (e.g. disruption to daily life), psychosocial well-being, quality of life and life expectancy. This situation, which is particularly difficult for patients who face uncertain pathways and unresolved anxiety about the future, is compounded by the fact that little is known about preferences for information sharing and the desire to engage in treatment decisions.

Objectives

This programme sought to address the deficits described above, the premise being that the provision of personalised evidence-based information at key decision points would facilitate treatment decisions, support clinical practice and improve patient experiences. The objectives were as follows:

- primary – to generate high-quality, longitudinal, real-world information about the care pathways of the general population of patients with chronic haematological malignancies, incorporating data on healthcare costs, and patient preferences for information sharing and engagement in treatment decisions
- secondary – to produce accessible information resources suitable for testing in routine NHS practice.

Design

This was a population-based cohort of ≈ 8000 patients with chronic haematological malignancies, incorporating 5 distinct, but inter-related, nested work packages with individual designs, including longitudinal studies, cross-sectional surveys, data linkage and qualitative investigation of patient experiences, as follows:

1. in-depth exploration of patient experiences: information and decision-making
2. population-based analyses
3. health economics
4. development of information resources to support decision-making
5. patient well-being and decision-making survey.

Setting

This programme is predicated on the established expertise and infrastructure of the UK's Haematological Malignancy Research Network (HMRN; www.hmrn.org), which was initiated in 2004 to provide robust, generalisable data to inform research and clinical practice. Set in Yorkshire and Humberside, HMRN's population of ≈ 4 million people has a comparable sex, age, urban/rural and area-based deprivation (Index of Multiple Deprivation, income domain) distribution to that of the UK. Within HMRN, clinical practice adheres to national guidelines, and all patients are centrally diagnosed (≈ 2500 each year), tracked through their care pathways and linked to nationwide health administrative databases (deaths, cancer registrations and Hospital Episode Statistics). HMRN also contains a general-population cohort linked to the same nationwide administrative databases as the patient cohort. HMRN has ethics approval (Leeds West Research Ethics Committee 04/Q1205/69) and Section 251 support [NHS Act 2006: Patient Information and Advisory Group 1-05(h)2007], which provides the legal basis for data collection/linkage. Research building on HMRN's infrastructure requires supplementary approvals, granted for this programme by the London, City and East Committee (Research Ethics Committee 16/LO/0740).

Participants

Participants were patients aged ≥ 18 years resident in the study area and diagnosed with one of the three commonest chronic haematological malignancies: chronic lymphocytic leukaemia, follicular lymphoma or myeloma.

Patient public involvement and engagement

Patient and public involvement and engagement is integral to HMRN, and lay individuals are routinely involved in all research activities via the Patient Partnership, which was established in 2009 and is overseen by a Partnership Committee comprising patients, relatives/carers and researchers. The Partnership includes several hundred people who have agreed to further contact for research purposes, including directing HMRN's activities and participating in surveys and individual/group discussions. HMRN also benefits from a group that act as a 'sounding board', ensuring that all our research is patient-centred and relevant. Patients and relatives were involved in the current programme as applicants and participants. Discussions preceding our application identified issues for investigation, based on patient experiences. Information was considered an area requiring improvement because of widespread concern about W&W and the anxiety and distress that this was said to instil due to uncertainty about 'if' and 'when' treatment may be required, and its likely impact. Such stories underpinned this programme, alongside our ability (via HMRN) to provide information, mapped to pathways.

Changes to programme

Following piloting, the survey instrument was split and the content expanded. Questionnaire 1 focused on quality of life and was to be completed pre appointment, and questionnaire 2 targeted treatment decisions and was to be completed post appointment. The number of in-depth interviews was finalised at 35 as the purposeful sampling strategy identified 'information-rich' sources and high-quality data. Finally, the secondary objective was curtailed by the COVID-19 pandemic (see *Conclusions*).

Results

Patient characteristics and treatment pathways

With a median diagnostic age of 71 years, chronic lymphocytic leukaemia and myeloma occur more frequently in men than in women. By contrast, with a younger median age of 65.5 years, follicular lymphoma has a slight preponderance among female patients. First-line management varied markedly by subtype; 84.7% of chronic lymphocytic leukaemia patients were monitored via W&W, compared with 40.9% with follicular lymphoma and 20.2% with myeloma. Furthermore, with a 5-year relative survival of 47.7%, patients with myeloma fared less well than those with chronic lymphocytic leukaemia (5-year relative survival 84.1%) or follicular lymphoma (5-year relative survival 88.1%). To quantify/visualise the data, two software applications were developed. First, a tree-based approach aggregated patients into pathway subgroups, beginning with the initial management or event (chemotherapy, observation or death) and ending with the last. Diversity by cancer subtype was clearly evident: among those diagnosed between 2004 and 2010 who were initially managed by W&W, 40.6% (419/1031) with chronic lymphocytic leukaemia, 38.4% (93/242) with follicular lymphoma and 26.5% (90/339) with myeloma were still on W&W at the end of follow-up (5–11 years later). Second, a patient pathway generator was developed in-house from a Data-Driven Documents (D3) JavaScript library (https://d3js.org/), followed by an iterative graphical restructuring algorithm that displayed visualisations of entire pathways that included all diagnoses, investigations, treatments/responses and hospital activity in real time (generation < 1 second).

Population-based analysis and prognostic model

Facilitating the identification of patients requiring alternative treatment strategies and separating those at high-risk of disease progression and/or transformation from those who are not is important for clinicians and patients. With a view to incorporating genetic data into conventional prognostic models and the future development of novel targeted treatments, we examined the mutational data of patients newly diagnosed with follicular lymphoma. The molecular investigations undertaken determined that aberrant somatic hypermutations played a leading role in the genetic substructure of follicular lymphoma, with a small number of key genetic mutations, including *STAT6*, having a marked impact on prognosis. These clusters have implications both for understanding pathogenesis and for potential future treatment strategies. However, separation of follicular lymphoma according to mutational status despite being linked to apparent underlying mechanistic differences provides only limited prognostic information in conventionally treated patients.

Hospital activity patterns

Patients often question the difference their disease, or treatment, is likely to have on their survival, future healthcare needs and quality of life. As expected, inpatient and outpatient Hospital Episode Statistics activity post diagnosis was considerably higher among patients with chronic haematological malignancies than in the general population, the largest differences being for myeloma. For all three diagnoses, hospital activity peaks around the time of diagnosis, outpatient activity remaining high but levelling around 12 months after diagnosis, and inpatient activity around 8 months post diagnosis for chronic lymphocytic leukaemia and 36 months for follicular lymphoma.

Health economics

A microsimulation model was developed for myeloma to reflect multiple lines of treatment, post-treatment surveillance and overall survival. The model was used to predict long-term costs, and quality-adjusted life-years to enable future assessment of the expected impact of new treatments and policies. Input parameters were estimated by analysing individual-level time-to-event data (to represent patients' trajectories), the EuroQol-5 Dimensions, five-level version (to derive quality-adjusted life-years), and HMRN treatment data (to model treatment sequences). Healthcare costs were estimated from Hospital Episode Statistics, based on national tariffs. The model is flexible enough to incorporate evidence from other sources, including clinical trials. Results were based on 2687 patients with myeloma, diagnosed 2004–15 and followed up until December 2017.

Patient survey

Two questionnaires for use in haemato-oncology outpatient clinics were developed in-house and piloted: questionnaire 1 (health-related quality of life) was to be completed before the clinic appointment, and questionnaire 2 (treatment decisions) was to be completed after. The survey was successfully implemented in all 14 HMRN hospitals, 2016–8, with 3153 patients participating, 1282 with chronic lymphocytic leukaemia, follicular lymphoma or myeloma. Providing information across the pathway, over half of patients completed questionnaires while on W&W; the remainder either received chemotherapy or were monitored post treatment. Survey distribution and data collection were found to be simple and effective, and patients said that they appreciated the opportunity to 'give back' via taking part in research.

Patient preferences for information sharing and engagement in treatment decisions

Interviews were conducted with 35 patients who had experienced varying treatment pathways, and 10 relatives. A large, rich data set generated multifaceted findings. The unpredictable nature of chronic haematological malignancies was confirmed, as were the challenges of coping with uncertain pathways. This caused prolonged anxiety, which could be more distressing than any physical symptoms and difficult to resolve because of infrequent clinic visits and an absence of definitive information. Preferences for information (timing, content, depth and format) varied markedly, both between patients and across individual pathways over time. Regarding treatment decisions, most interviewees said that they preferred a discussion about options, but did not wish, or felt ill-equipped, to make choices themselves. Finally, individual access to a support network (e.g. family, friends or clinical staff) was found to impact positively on experiences and preferences.

Conclusions

Enhancing understanding about the pathways of the general population of patients with chronic haematological malignancies, this programme has accrued an abundance of new evidence. Data collection instruments have been developed, pathway visualisation programmes have been written, and detailed quantitative and qualitative information, to an extent not previously captured, are now available. We have demonstrated that it is possible to distribute questionnaires and collect longitudinal data in hospital settings, and assemble, summarise and visualise longitudinal pathways, including data on diagnostics, prognostics, treatments, transformations/progressions, hospital episodes, outcomes and costs. Regarding health economics, we have shown the utility of using longitudinal data to estimate how many patients are on each treatment line, post treatment after each line, receiving palliative care, and so on, thereby facilitating cost calculations and resource planning. Such models could potentially be used by commissioners and healthcare managers to simulate the impact of novel policies, treatments and pathway changes prior to their introduction.

The marked, ongoing anxiety experienced by some patients due to uncertain pathways suggests that benefits could be accrued from increased awareness about the extent and impact of this, alongside interventions to counteract such difficulties. Addressing varied preferences for information (content,

depth, format and timing) would require a broad range and depth of material (from a basic overview to detailed options), complexity (from simple terminology to more complicated graphs) and methods for sharing (verbal, written or electronic), thereby enabling patients to access what they want to know, when they want to know it. As most (but not all) people reported a preference for clinicians to make treatment recommendations, this should also be considered. Changing preferences means that strategies for patient engagement with information-sharing and treatment decisions may need to be tailored to individual needs over time, assessed by routine clinician monitoring. Clinicians might also explore the social infrastructure and support network available to patients, so that they are aware of gaps that could be addressed.

Based on several thousand patients, and exceeding any evidence previously generated, this programme collated, assessed and successfully mapped high-quality evidence-based information about the pathways of the general population of patients with chronic haematological malignancies. Previously lacking, these data, coupled with new evidence on preferences for information-sharing and treatment decisions garnered directly from patients, provide the foundation to improve clinical practice. Unfortunately, the final part of the programme could not be completed due to the COVID-19 pandemic; hence, the key future priority is the translation of the data accrued into accessible information resources suitable for testing in routine NHS practice. These would need to be responsive to both the rapidly changing haemato-oncology landscape and the varying needs of clinicians and patients at different points on the pathway. Building on the foundations of the present programme, future research, in collaboration with clinicians and patients, could include:

1. co-refinement of electronic visualisations for use in multidisciplinary team settings
2. co-design of resources for use in clinician–patient consultations
3. development of cluster randomised trial protocols to test resources developed in (1) and (2) across a single multidisciplinary team area using the data collection instruments developed, prior to further evaluation within/outside the region.

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