Assessment and reporting of quality-of-life measures in pivotal clinical trials of hematological malignancies

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Abstract:

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Clinical trial registration information (if any):
Studies that supported FDA hematological drugs approvals

January, 2016 - May, 2020

(n=52)

Primary, secondary and exploratory endpoints reported in study protocols reviewed

No measurement of patient reported outcomes or health related quality of life

(n=28)

One or more measurement of patient reported outcomes or health related quality of life

(n=24)

Measurement reported in initial publication (n=5)

Measurement reported in a subsequent publication/conference presentation (n=14)

Measurement not reported (n=5)
Research Letter

Assessment and reporting of quality-of-life measures in pivotal clinical trials of hematological malignancies

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**Keywords:** Hematological malignancies; multiple myeloma; leukemia; lymphoma; myelodysplastic syndrome; quality of life; HRQOL; patient experience.

**Conflict of interest:**

HEH is a co-founder with equity in Allovir and Marker Therapeutics, has served on advisory boards for Novartis, Gilead, Tessa Therapeutics, PACT Pharma and Mesoblast and received research support from Tessa Therapeutics and Kuur Therapeutics.

Portions of this study were presented at the American Society of Clinical Oncology Quality Care Symposium Meeting in 2020 and the Society of Hematologic Oncology Annual Meeting in 2020.
Introduction

To accurately evaluate the benefit of new cancer treatments, clinical trials must assess health-related quality of life (HRQOL) measures, as well as safety and antitumor efficacy. HRQOL measures reflect the physical and mental health of patients and are particularly important in hematological malignancies, where some interventions have modest survival benefits but significant toxicities. Thus, studying how various hematologic malignancies and their treatment impact HRQOL is crucial to determining the best management strategies. Here, we analyzed the extent to which the field appreciates the value of HRQOL in pivotal clinical trials by calculating how often trials for drugs to treat hematological malignancies that resulted in Food and Drug Administration (FDA) approval assessed patient quality of life (QOL).

Methods

We obtained data on HRQOL from study protocols (available at https://clinicaltrials.gov/) and publicly available product labeling at Drugs@FDA. We analyzed drugs approved between January 2016 and May 2020 to reflect the most recent hematologic malignancies drug approvals. The studied hematologic malignancies included multiple myeloma, leukemias, non-Hodgkin lymphomas, Hodgkin lymphoma, and myelodysplastic syndrome. We reviewed primary, secondary, and exploratory outcome measures in each protocol. If any QOL measurement was included as part of the primary, secondary, or exploratory outcomes in the study protocol, we deemed this study to assess HRQOL. Only 69% of clinical trials had some results reported in clinicaltrials.gov. Therefore, for the studies that collected data on HRQOL, we
systemically searched of PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and the bibliographies of the relevant articles using the National Clinical Trial (NCT) number, study title/subtitle, authors names and/or studied drug/s to ascertain whether the published studies that supported FDA drug approval reported QOL measures. To assess reporting of HRQOL, we analyzed all publications available by February 10, 2021 (our data analysis cut-off point). Each drug approval had at least one available publication or abstract presentation. The frequency of HRQOL assessment and subsequent reporting of HRQOL measures were analyzed.
Results

We examined a total of 52 clinical trials conducted in the studied period. These trials enrolled 16,246 patients, supporting 49 drug approvals. Only 24/52 (46%) of the clinical trials included at least one HRQOL metric as part of their endpoints. Of those trials, only 19 (79%) provided data on their measured HRQOL parameters (Figure 1). Of the clinical trials that reported measured HRQOL metrics, 26% (5/19) included them within the initial publication, while 74% (14/19) reported them in a different publication or at a conference or meeting (Table 1). In leukemias, chronic myeloid leukemia and acute lymphoblastic leukemia collected and reported HRQOL in 75% of clinical trials, whereas none of the trials supporting acute myeloid leukemia drug approvals collected HRQOL metrics. In multiple myeloma, 57% of clinical trials collected and reported an HRQOL metric. In lymphomas, only T cell lymphoma trials collected and reported HRQOL metrics more than half of the time. Most clinical trials that collected HRQOL metrics used either one metric (38%) or 2 metrics (54%); only 2 clinical trials (8%) used 3 metrics. The most commonly used metrics were the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) and the EuroQol 5 Dimension 5 (EQ-5D) survey. There was no statistically significant trend for improved collection or reporting of HRQOL over time. The trials that collected at least one HRQOL metric but did not report it (n=5) tended to be more recent (2 trials in 2018, 1 trial in 2019, and 2 trials in 2020).
Discussion

Patient-reported outcomes (PROs), including HRQOL measures, are becoming an integral part of patient assessment in oncology clinical research and clinical practice. The use of HRQOL tools can facilitate the assessment of outcomes that are important to patients. Such measures can help capture patient experiences outside of their clinical visits and the impact of studied drugs on their daily life. These data will help patients and their physicians to choose the optimal available treatment. Common types of PRO measures include rating scales and counts of events. The FDA published guidance describing how to implement PROs. Though helpful in describing the process of PRO implementation, their guidance does not establish legally enforceable responsibilities. In 2020, the FDA Oncology Center of Excellence launched Project Patient Voice, a pilot project collecting patient-reported symptom data from clinical trials supporting FDA approval for certain cancer drugs. The goal of this project is to enable patients and their doctors to make better decisions, as these symptom data are not usually included on drug labels but can provide valuable additional information.

A previous report indicated lower functioning scores and higher symptom burden scores in hematological malignancy survivors compared to population controls, suggesting HRQOL are especially important in this patient cohort. Our analysis revealed that HRQOL measures have been understudied in clinical trials leading to FDA drug approval in hematological malignancies. Less than a half of the 52 studies we analyzed measured HRQOL, and most of those didn’t report the results of HRQOL measures in the initial publication. This problem is relevant to oncology more broadly, as only a minority of new oncology drugs authorized by the European Medicines Agency (EMA) from 2009-2013 were approved with evidence of improved QOL. Indeed, most
oncology studies published in three high-impact journals were found to assess QOL only during the intervention phase, with a minority (3.4%) of studies assessing QOL until time of death.\(^7\)

Despite the limited number of well developed, disease-specific instruments to measure HRQOL, multiple validated tools are available. The EORTC QLQ-C30\(^8\) and the Functional Assessment of Cancer Therapy — General (FACT-G) questionnaire are frequently used. The EORTC QLQ-C30 is designed to use in multiple cancers and it is intended to be supplemented by cancer-specific questionnaire modules or supplements. For example, the EORTC QLQ – MY20 is a cancer-specific questionnaire used in multiple myeloma. Hematological malignancy-specific tools to evaluate HRQOL in clinical trials are being developed.\(^9,10\) The FACT–Leukemia (FACT-Leu) is a newly validated 27-question tool that can be used in acute or chronic leukemia patients regardless of eligibility for intensive therapy.\(^10\) The availability of validated disease-specific validated tools will help to standardize the process of QOL reporting.

The lack of collection and reporting of HRQOL measures in hematological malignancies may be related to an underappreciation of their significance or the fact that they are not required for drug approval. However, broader availability of HRQOL will enable patients to choose the best therapy for their treatment goals as well as their lifestyle.

One caveat to this study is that we included only clinical trials that led to FDA approval, as they represent the drugs with the best current evidence of activity. HRQOL results from more recent studies may need more time to be analyzed and may be reported later in separate publications. Nonetheless, as clinical trials have changed the treatment paradigm for most hematological malignancies, more frequent assessment and reporting of HRQOL in these diseases is needed. Overall, more robust and reliable HRQOL data will improve patient care.
Therefore, we believe clinical trials should be required to collect HRQOL data and report them as part of the FDA approval application.

**Data sharing statement**

For data sharing, contact the corresponding author: samer.alhadidi@bcm.edu

**Author contribution**

S.A. designed research, performed research, contributed vital new reagents or analytical tools, analyzed data, and wrote the paper. R.K., G.C, H.H., and C.R. analyzed data and wrote the paper.

**Figure legends**

**Figure.1** Flowchart of studied clinical trials

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**Table 1** Frequencies of analyzed clinical trials.

| Disease | Number of trials | Number of patients enrolled in all studies | Number (%) of study protocols that assessed PRO and/or HRQOL | Number (%) of reported PRO/HRQOL | PRO or HRQOL measure/s used by clinical trials |
|---------|------------------|-------------------------------------------|-------------------------------------------------------------|----------------------------------|-----------------------------------------------|
| Disease                  | Patients | HRQOL Score | Minimum - Maximum | Mean (SD) | Median (IQR) | Scoring System(s)                          |
|--------------------------|----------|-------------|-------------------|-----------|--------------|-------------------------------------------|
| **Leukemia**             |          |             |                   |           |              |                                           |
| Chronic lymphoid leukemia| 26       | 7262        | 34-717            | 10 (38)   | 8 (31)       | FACT-Leu, EORTC QLQ-C30, EQ-5D-3L, QLQ-CLL16 |
| Chronic myeloid leukemia | 4        | 854         | 51-487            | 3 (75)    | 3 (75)       | FACT-Leu, EORTC QLQ-C30, EQ-5D-3L          |
| Acute lymphoid leukemia  | 4        | 922         | 75-405            | 3 (75)    | 3 (75)       | PedsQL, EORTC QLQ-C30, EQ-5D               |
| Acute myeloid leukemia   | 9        | 2312        | 34-717            | 0 (0)     | 0 (0)        | n/a                                        |
| Hairy cell leukemia      | 1        | 80          | n/a               | 0 (0)     | 0 (0)        | n/a                                        |
| **Lymphoma**             | 18       | 5212        | 80-1334           | 9 (50)    | 7 (39)       |                                           |
| Hodgkin lymphoma         | 3        | 1639        | 95-1334           | 2 (66)    | 1 (33)       | EORTC QLQ-C30                              |
| Diffuse large B cell lymphoma | 3 | 281        | 80-108            | 1 (33)    | 1 (33)       | FACT-Lym, SF-36                            |
| Mantle cell lymphoma     | 2        | 210         | 86-124            | 1 (50)    | 1 (50)       | EORTC QLQ-C30                              |
| Follicular lymphoma      | 6        | 2300        | 83-1202           | 3 (50)    | 2 (33)       | FACT-Lym, EQ-5D                            |
| Primary mediastinal B cell lymphoma | 1 | 53        | n/a               | 0 (0)     | 0 (0)        | n/a                                        |
| T cell lymphoma          | 3        | 729         | 131-372           | 2 (66)    | 2 (66)       | FACT-G, EQ-5D, Skindex-29                   |
| **Multiple myeloma**     | 7        | 3543        | 122-1085          | 4 (57)    | 4 (57)       | EORTC QLQ-C30, EQ-5D, FACT-MM, QLQ-MY20    |
| Myelodysplastic syndrome | 1        | 229         | n/a               | 1 (100)   | 0 (0)        | EORTC QLQ-C30                              |
| **Total**                | 52       | 16246       | 34-1334           | 24 (46)   | 19 (37)      |                                           |

**HRQOL**, health-related quality of life; **PRO**, patient reported outcome; **n/a**, not applicable.