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Review

Patient-reported outcomes in acute myeloid leukemia: Where are we now?☆

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ABSTRACT

Outcomes for acute myeloid leukemia remain poor, and treatment decisions must consider not just quantity, but also quality of life (QOL). We conducted a systematic review of studies in patients with acute myeloid leukemia or high-risk myelodysplastic syndrome that incorporated patient-reported outcome (PRO) measures. PubMed and PsycINFO were searched for articles published from January 2000 through June 2016. Forty-one were relevant for our review with more published in recent years. There was considerable inter-study heterogeneity in which instruments were used, and many studies employed multiple (often overlapping) instruments. Longitudinal studies in particular suffered from both high attrition rates due to disease-related mortality as well as waning compliance with questionnaire completion. There remain significant challenges to incorporation of PROs into leukemia trials. Despite these limitations, however, well-implemented PROs can provide important information beyond objective response outcomes and highlight areas of focus for clinicians caring for patients and for future research endeavors.

1. Introduction

Acute myeloid leukemia (AML) continues to have a poor prognosis, often requiring aggressive treatments, including combination chemotherapy, for cure. Unfortunately, many cases of AML are refractory to or relapse despite these intensive treatments, and often survival is measured in months. Ideally, decisions about whom to treat and how aggressively to pursue a cure should involve weighing the likelihood of success against potential harms. Similarly, evaluation of treatment efficacy should take into account both the beneficial effects on the disease and the potentially harmful effects on the patient. One way to assess this balance is by evaluating patient-reported outcomes (PROs) and incorporating these measures into clinical trials. Increasingly, PROs (rather than physician-reported outcomes) are considered to be the "gold standard" for capturing symptomatic adverse events [1].

A systematic review on the use of PROs in randomized controlled trials in patients with leukemia revealed that only four such trials conducted in AML patients had been published between 2007 and 2014 [2–6]. However, PROs have also been incorporated into non-randomized observational and interventional AML studies, and these trials have not yet been catalogued or analyzed in a systematic way. In order to better understand the role that PROs play in AML studies and explore areas for growth in this field, we sought to conduct a systematic review of studies published since 2000 in which PROs were collected from AML patients. Additionally, we included studies of patients with high-risk myelodysplastic syndrome (MDS), as the natural history and treatment of this disorder is similar to that of AML [7]. Our aims were to summarize the current use of PROs in the field and to identify challenges to greater implementation and interpretation that would benefit from further research.

2. Methods

All studies of patients diagnosed with AML or high-risk myelodysplastic syndrome (MDS) were included provided that patients were age 18 and older and PRO assessments were self-administered. High-risk MDS was defined as MDS with excess blasts or MDS treated with AML-like chemotherapy. Studies on acute promyelocytic leukemia (APL) were excluded, as were studies involving any patients with other diagnoses (e.g., acute lymphoblastic leukemia) and studies exclusive to HCT patients. A systematic PubMed and PsycINFO literature review of English-language articles published between January 2000 and June

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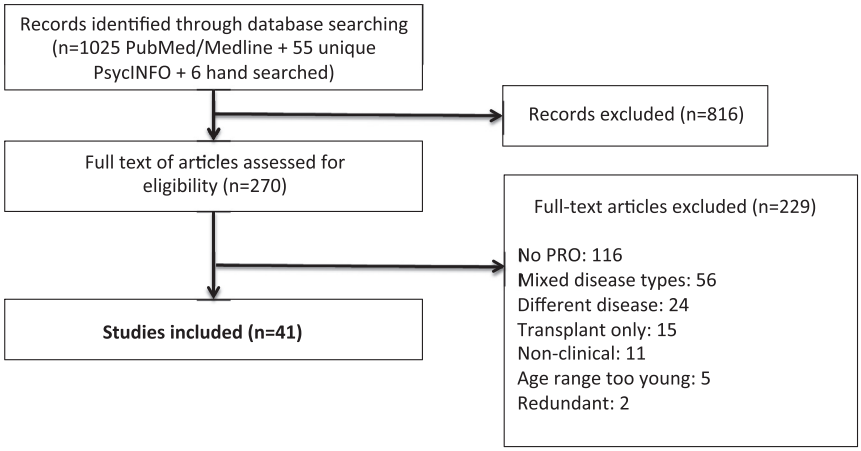

Fig. 1. PRISMA flow diagram.

2016 was undertaken according to PRISMA guidelines [8], with search strategy detailed in Supplementary Table 1. Titles and abstracts were screened, and references were hand-searched for additional papers; final inclusion was based on full manuscript review. Screening was performed by S.A.B. and K.K., with disputes resolved by G.H.L. The following data were extracted: trial demographics, patient demographics, data on patient enrollment, details of PRO assessment, extent and analysis of missing data, and results. Data completeness at baseline was determined as a percentage of eligible patients approached for study enrollment that completed initial PRO. For longitudinal studies, data completeness was determined as a percentage of surviving patients who completed PRO assessment at each time point. Study quality was assessed using the Mixed Methods Appraisal Tool (MMAT) [9], which was chosen for its ability to evaluate both qualitative and quantitative studies.

3. Results

The initial search yielded 1025 results from PubMed, 55 unique results from PsycINFO, and 6 additional after hand search. Among these, 270 qualified for full text review and 41 met inclusion criteria (Fig. 1) [3,5,10–53]. There was a clear trend towards increasing numbers of studies with PRO endpoints published over time, particularly since 2011 (Fig. 2). Instruments measuring overall QOL were used more frequently than symptom-directed questionnaires (Fig. 3); the most commonly used instrument was the EORTC QLQ-C30 (including foreign language versions), employed in 23 studies [54]. Most studies using questionnaires to assess PROs relied on multiple instruments (median 2, range 1–4), often assessing overlapping symptoms. In addition, 8 of these studies used single-item scales to measure specific symptoms, again often with some redundancy. For example, all of the 6 studies that assessed fatigue as a single item [5,10,24–26,36] included at least one other measure of fatigue, including multiple items from the EORTC QLQ-C30 or the FACT fatigue module. None of the studies employing multiple questionnaires reported the time required to complete all instruments.

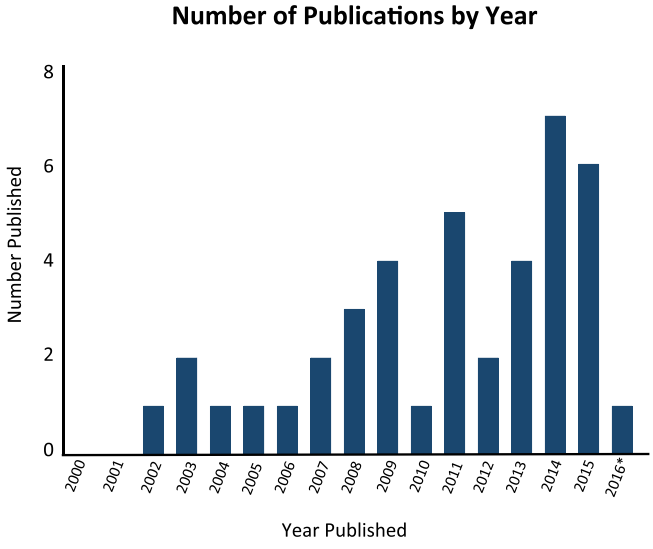

Fig. 2. Number of AML publications per year involving PROs. Data for 2016 represents only the first 6 months of the year.

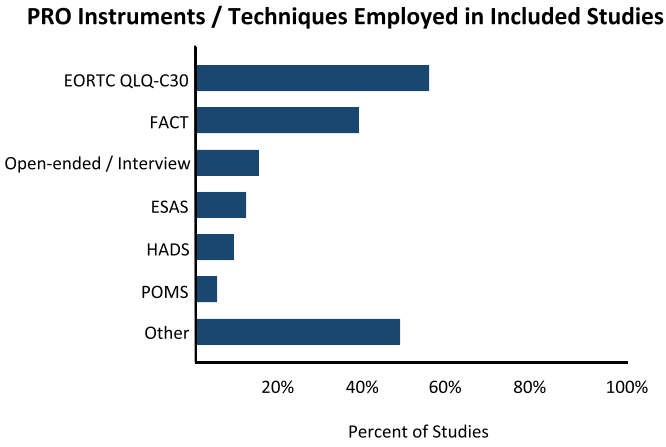

Fig. 3. Prevalence of PRO instruments employed in included studies. Total percentage sums to > 100% as some studies used more than one instrument.

3.1. Methodological quality in included studies

The overall quality score was 100% (4 of 4 criteria met) in 28 studies (68%), 75% in 9 (22%), and 50% in 4 (10%), as shown in Table 1. The most common cause for down-grading in the quality assessment was low or unclear extent of missing data or patient drop-out. Among longitudinal studies, the proportion of surviving patients with missing PRO data increased over time, with compliance over 80% for the first few months, dropping to 60% after month 6 (Fig. 4). Most studies did not describe adequate methods for handling missing data: 68% did not discuss the issue at all, and 9% either restricted analysis to patients with complete data or assumed data to be missing at random and proceeded without it; among the remaining studies, 2 compared characteristics of patients who did and did not have missing data [16,37] and 6 imputed missing data [5,10,13,20,29,50]. A major impediment to longitudinal QOL reporting in AML studies is the high rate of attrition due to disease-