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Health-related quality of life and symptom assessment in randomized controlled trials of patients with leukemia and myelodysplastic syndromes: What have we learned?

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ABSTRACT

Health-related quality of life (HRQOL) and other patient-reported outcomes (PROs) are crucial for a comprehensive evaluation of treatment effectiveness. A systematic review of randomized controlled trials (RCTs) with a PRO endpoint conducted in patients with leukemia and myelodysplastic syndromes (MDS) was performed. Eligible studies were evaluated independently, according to a pre-defined coding scheme, by two reviewers. Thirteen RCTs, enrolling overall 3380 patients were identified. There were four RCTs involving acute myeloid leukemia patients (AML), one with acute lymphoid leukemia (ALL), five with chronic lymphocytic leukemia (CLL) and three with MDS. Six RCTs accurately documented PRO methodology assessment and were thus considered likely to robustly inform clinical decision-making. Of these, three RCTs dealt with AML, two with CLL, one with MDS. A growing number of RCTs in leukemia and MDS have included a PRO component in recent years. Inclusion of PROs in RCTs is feasible and can provide unique information to facilitate clinical decision-making.

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1. Introduction

Despite major therapeutic advances in past decades, there remains significant variation in long term outcomes in leukemia and myelodysplastic syndromes (MDS). Long-term survival rates for chronic myeloid leukemia (CML) and acute promyelocytic leukemia (APL) have now exceeded 80% (Kantarjian et al., 2012; Bjorkholm et al., 2011; Watts and Tallman, 2014) due to the administration of new agents targeted to oncogeneic markers. Chemoimmunotherapy combinations for chronic lymphocytic leukemia (CLL) have led to an increase in quality of responses and prolonged survival rates from 46% up to 75% over the past two decades (Tam et al., 2008; Woyach et al., 2013; Kristinsson et al., 2009; Brenner et al., 2008). Modern intensive regimens and transplant options have yielded 5-year survival rates ranging from 30% to 50% in younger patients with acute myeloid or lymphoid leukemia (Pulte et al., 2009; Goldstone et al., 2008; Pidala et al., 2011; Marks, 2010), but treatment of elderly acute leukemia or of "unfit" patients remains a challenge (Juliusson et al., 2009; Burnett, 2012). Finally, lenalidomide, azacitidine, and decitabine were shown to provide some clinical advantages among MDS patients, resulting in new standards of care for these patients who have limited access to intensive treatments especially if they are old and with comorbidities (Garcia-Manero, 2014; Malcovati et al., 2013).

However, a comprehensive evaluation of treatment effectiveness should also consider the patient burden of the disease and treatment effects (Bardes, 2012; Basch et al., 2012). Based on this patient-centered care model, patient-reported outcomes (PROs), as direct collection of patients' perception on their own health status condition, can provide valuable information that complement traditional clinical outcomes (Alibhai et al., 2007; Efficace et al., 2013; Eichhorst et al., 2007; Koenigsmann et al., 2006; Schumacher et al., 1998; Sekeres et al., 2004). The extent to which PROs can help better inform clinical decision-making also depend on the quality of PROs design in the research protocol and on the accuracy of reported outcomes in final study reports. Failure to address key methodological issues in health related quality of life (HRQoL) research could undermine translation of research findings into clinical practice applications. (Brundage et al., 2011; Efficace et al., 2007a; Calvert et al., 2013).

Despite international guidelines on leukemia and MDS indicating the importance of incorporating HRQoL in the healthcare evaluation process (Malcovati et al., 2013; Appelbaum et al., 2007; Baccarani et al., 2013; Eichhorst and Hallek, 2007; Hallek, 2007), PRO inclusion in randomized controlled trials (RCTs) of leukemia and MDS patients remains scarce (Caocci et al., 2009; Efficace et al., 2008).

A previous systematic review on studies published between 1980 and 2007, PRO assessment in RCTs of patients with leukemia and MDS showed a number of methodological drawbacks in the trial design and PRO reporting (Caocci et al., 2009; Efficace et al., 2008). Given the growing interest of the scientific community and regulatory stakeholders in the use and application of PROs (PCORI, 2012; US Food and Drug Administration, 2009; European Medicine Agency, 2014), we have undertaken a systematic review to examine use of PROs in leukemia and MDS in recently published RCTs.

The primary objective of this study was to identify the number of RCTs with a PRO endpoint in leukemia and MDS published since 2007 following on from the previous systematic reviews (Caocci et al., 2009; Efficace et al., 2008). Secondary objectives were to examine whether the standard of PRO reporting has improved over time and to synthesize major evidence from RCTs most likely to robustly inform clinical decision-making.

2. Material and methods

2.1. Search strategy for identification of studies

A systematic literature search for study meeting the criteria was undertaken on electronic databases: PubMed/Medline, the Cochrane Controlled Trial Registry, PsycINFO, and PsycARTICLES from August 2007 to October 2014. Key researching strategy is reported in the Appendix A. The search strategy for PubMed/Medline was restricted to RCTs. Only English language article were selected and no restrictions were included in the search field description. Titles and abstract of identified articles were screened for inclusion. Additional publications were identified from reference lists of relevant articles. Details on the search strategy and selection process were documented according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guideline (Moher et al., 2009).

2.2. Criteria for study selection

Adult patients with a diagnosis of MDS or leukemia were included regardless of their own sub-classification category or their age at diagnosis. Adult survivors to acute leukemia treated in pediatric age were eligible as well as patients diagnosed in their adulthood. RCTs dealing with psychosocial interventions were excluded. Only RCTs including PROs as an endpoint of the study were considered. Studies exclusively using proxy-based questionnaire were excluded. No restriction was made with regard to the number of patients enrolled. Conference abstracts were excluded due to their lack of necessary information to assess quality of PRO reporting.

2.2.1. Data extraction and type of information analyzed

Data extracted from each RCT were collected in a predefined electronic data extraction form. Two reviewers (M.J. and L.C.) independently extracted data on: (1) basic trial demographics (e.g., year of publication, journal); (2) clinical and PRO characteristics (e.g., number of patient enrolled, study location, treatments being compared, PRO instrument used, schedule of clinical and PRO assessment, summary of clinical and PRO findings); (3) the quality of PRO reporting, based on the recently published guidelines by the International Society for Quality of Life Research (ISOQOL) (Brundage et al., 2013). Results were crosschecked and discrepancies were resolved by reviewers revisiting the paper and discussing with a senior author (G.C. or F.E.). In studies with multiple publications, relevant data were obtained by combining all trial-related publications.

2.2.2. Quality assessment and identification of main PRO evidence

Quality of PRO reporting was assessed according to the ISOQOL consensus-based recommendations for reporting PRO data (Brundage et al., 2013). These recommendations were developed by a large international panel of experts and represent the highest quality criteria that also informed the development of the CONsolidated Standard of Reporting Trials (CONSORT) PRO guidelines (Calvert et al., 2013). The ISOQOL recommendations include up to 29 important issues that studies should document in order to provide readers with a critical appraisal of PRO findings. These issues are related to specific details that should be reported in the publication and include, for example: identifying in the abstract that PRO was a primary or secondary outcome of the study; documenting the PRO hypothesis; reporting evidence of the use of a validated PRO instrument; specifying the methods of PRO administration; indicating the extent of PRO missing data during the study period and specifying methods used to address PRO missing data in the statistical analysis.