Poster PCN300

Systematic Literature Review of Patient-Reported Outcome Measures Used in Mantle Cell Lymphoma

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INTRODUCTION

- Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin's lymphoma (NHL), representing approximately 3% of NHL cases.[1] MCL is associated with a poor prognosis due to its aggressive clinical nature, low sensitivity to traditional chemotherapy, and high relapse rates[2,4]; median age at diagnosis is 67 years.[4]
- At this time, MCL is considered incurable with conventional chemotherapy.[2] Given that patients with MCL are often administered aggressive therapy,[2,3] physicians have the responsibility to ensure that their patients are not only receiving the best evidence-based treatment, but at the same time, that they are considering their patients' wishes and mental-emotional health.
- Quality of life (QoL) as measured by patient-reported outcomes (PROs) is recognized by clinicians to include important indicators for lymphoma patients, both in terms of clinical management and cost-benefit evaluation of therapies.
- Identifying and understanding the proper use of PROs in this disease area is necessary to provide the best possible treatment options to patients with MCL.

OBJECTIVES

- The objective of this systematic literature review was to 1) identify PRO instruments utilized in studies of patients with MCL to advance our understanding of the effects of MCL treatments on patients' QoL; and 2) descriptively summarize key PRO findings associated with commonly used MCL treatments.

METHODS

- A targeted systematic review of Medline, Embase, and gray literature (Google, Google Scholar) was conducted between January 01, 1999, and July 31, 2019.
- Eligibility and selection of studies (see **Table 1** for eligibility criteria for inclusion/exclusion of studies) were assessed by two reviewers independently through title, abstract, and full text screening per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5]
- A list of comprehensive search criteria was developed to include acronyms and variations of terms surrounding "patient-reported outcomes", "QoL", and "mantle cell lymphoma."
- Eligible studies were summarized descriptively by (a) type of PRO instrument and (b) treatments for MCL.

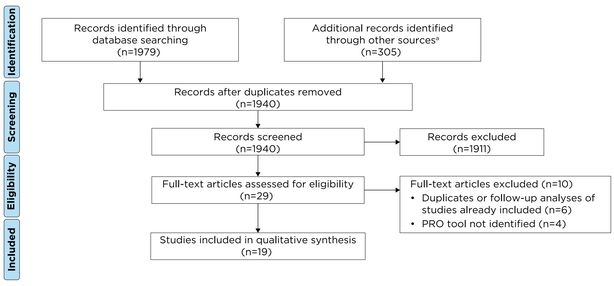
Table 1. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• Mantle cell lymphoma • All ages • Clinical trials and real-world evidence • All PRO tools • All levels of fitness • All lines of therapy • All genders • Global studies	• PRO instruments used in disease areas outside of MCL • Studies unavailable in the public domain • Non-English publications • Pre-clinical studies • Non-human studies

RESULTS

Summary of Studies Included in Literature Review

Figure 1. PRISMA Flow Chart



*Google and Google Scholar.

Table 2. Description of Studies Meeting Inclusion/Exclusion Criteria

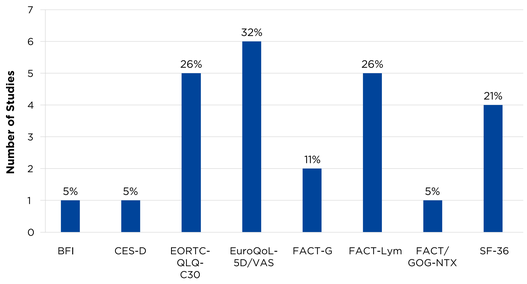
Authors	Title	Treatment Regimen(s)	Line of Therapy	Age	PRO Tool
Chemotherapy					
Hofmeister, et al. (2010)[6,a]	Phase I study of vorinostat (SAHA) after autologous transplant for patients with high risk lymphoma	• Vorinostat after BEAM-conditioned autologous transplant	2L+	Median, 59 (Range, 25-75)	CES-D BFI FACT-G
Novik, et al. (2011)[7]	Dichotomous model to evaluate treatment outcomes in non-Hodgkin's lymphoma patients	• Conventional chemotherapy (CHOP, CHOP-like regimens)	NA	Mean, 30.2 (SD, 13.5)	SF-36
Schenkel, et al (2014)[8]	Patient-reported experiences with treatment of chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL): Results of a quantitative survey	• IV chemotherapy	1L and 2L+	92% <65 years	EQ-5D
Shin, et al (2016)[9]	Results of a phase II study of vorinostat in combination with intravenous fludarabine, mitoxantrone, and dexamethasone in patients with relapsed or refractory mantle cell lymphoma: an interim analysis	• V-FND	2L+	Median: 67 (Range, 49-75)	EORTC QLQ-C30
Chemoimmunotherapy					
Burke, et al (2012)[10,11]	Differences in quality of life between bendamustine plus rituximab compared with standard first-line treatments in patients with previously untreated advanced indolent non-Hodgkin lymphoma or mantle cell lymphoma	• Bendamustine+ RTX (BR) • R-CHOP/R-CVP	1L	Not reported	EORTC QLQ-C30
Kim, et al (2009)[12]	Treatment outcome and quality of life in non-Hodgkin's lymphoma of intestine: a multicenter study of the Consortium for Improving Survival of Lymphoma (CISL)	• Surgery+ chemotherapy/CIT (CHOP, R-CHOP) • Chemotherapy/CIT alone	NA	Median, 55 (Range, 15-92)	EORTC QLQ-C30
Rosenthal, et al (2014)[13]	A phase II clinical trial of rituximab, cyclophosphamide, bortezomib, and dexamethasone (R-CyBor-D) in relapsed low grade and mantle cell lymphoma	• R-CyBor-D	2L+	Median, 69 (Range 51-80)	FACT/ GOG-NTX
Ruan, et al. (2010)[14]	Durable responses with the metronomic rituximab and thalidomide plus prednisone, etoposide, procarbazine, and cyclophosphamide regimen in elderly patients with recurrent mantle cell lymphoma	• PEP (C3)+RTX+low-dose thalidomide (RT-PEP(C3))	2L+	Median, 68 (Range, 52-81)	FACT-G
Tajima, et al. (2015)[15]	Examination of the prognosis and health-related quality of life of elderly patients with malignant lymphoma	• Modified R-CHOP (dose-modified R-CHOP or R-miniCHOP)	NA	Median, 85	SF-36
Targeted Therapy					
Andorsky, et al. (2014)[16,a]	MAGNIFY: A phase 3B, randomized trial of lenalidomide plus rituximab induction and maintenance therapy followed by lenalidomide single-agent versus rituximab maintenance in patients with relapsed/refractory indolent non-Hodgkin lymphoma (NHL)	• Lenalidomide+RTX followed by lenalidomide single-agent vs RTX maintenance	2L+	NA	FACT-Lym
Andrade Campos, et al. (2013)[17]	RIT with 90Y ibritumomab tiuxetan: long-term follow-up outcomes in B-cell NHL	• Ibritumomab tiuxetan	1L and 2L+	Mean: 65.75 (Range, 39-85)	SF-36
Cuyun Carter, et al. (2009)[18]	Validation of the EuroQol EQ-5D in patients with relapsed/refractory mantle cell lymphoma (RR MCL)	• Enzastaurin	2L+	Median, 66	EQ-5D
Hess, et al. (2017)[19]	Health-related quality of life data from a phase 3, international, randomized, open-label, multicenter study in patients with previously treated mantle cell lymphoma treated with ibrutinib versus temsirolimus	• Ibrutinib • Temsirolimus	2L+	NA	FACT-Lym EQ-5D-5L
Mela Osorio, et al. (2017)[20]	Impact on quality of life (QoL) of patients with chronic lymphocytic leukemia and mantle cell lymphoma under ibrutinib treatment: Preliminary data from a real world prospective project (pilot study)	• Ibrutinib	1L and 2L+	Median, 75 (Range, 51-84)	EQ-5D
Ruan, et al. (2015)[21]	Multi-centre phase II study with lenalidomide plus rituximab as initial treatment for mantle cell lymphoma: survival update and health-related quality-of-life analysis	• Lenalidomide+RTX	1L	Median, 65	FACT-Lym
Rule, et al. (2015a)[22]	Ibrutinib for the treatment of mantle cell lymphoma (MCL): Evaluating the correlation between patient-reported outcomes and durability of response in a phase 2 study	• Ibrutinib	2L+	NA	FACT-Lym
Rule, et al. (2015b)[23]	Quality of life in relapsed/refractory mantle cell lymphoma patients treated with lenalidomide vs investigator's choice: MCL-002 (SPRINT) trial	• Lenalidomide • Single-agent investigator's choice	2L+	NA	EORTC QLQ-C30
Witzens-Harig, et al. (2009)[24]	Quality of life during maintenance therapy with the anti-CD20 antibody rituximab in patients with B cell non-Hodgkin's lymphoma: Results of a prospective randomized controlled trial	• RTX maintenance • Observation only	2L+	Mean, 54.6	EORTC-QLQ-C30 EQ-5D EQ-5D-VAS
Other					
Hanf, et al. (2016)[25,a]	The REFRACT-LYMA cohort study: a French observational prospective cohort study of patients with mantle cell lymphoma	• Any regimen	1L and 2L+	>18 years	SF-36 EQ-5D FACT-Lym

1L, first line; 2L+, second line or later; BFI, Big Five Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CHOP, cyclophosphamide, doxorubicin HCl, vincristine sulfate, prednisone; CT, chemotherapy; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol-5-Dimensions; EQ-5D-5L, EuroQol-5-Dimensions 5-Level (©EuroQol Research Foundation. EQ-5D™ is a trademark of the EuroQol Research Foundation); FACT-G, Functional Assessment of Cancer Therapy – General; FACT-Lym, Functional Assessment of Cancer Therapy - Lymphoma subscale; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group neurotoxicity subscale; PEP (C3), prednisone, etoposide, procarbazine, cyclophosphamide; NA, not applicable or not available; R-CHOP, rituximab, cyclophosphamide, doxorubicin HCl, vincristine sulfate, prednisone; R-CVP, rituximab, cyclophosphamide, vincristine sulfate, prednisone; R-CyBor-D, rituximab, cyclophosphamide, bortezomib, dexamethasone; R-miniCHOP, attenuated R-CHOP regimen; SD, standard deviation; SF-36, 36-Item Short Form Survey; V-FND, vorinostat, fludarabine, mitoxantrone, dexamethasone; VAS, visual analog scale.

A PRO instrument was reported, but the publication did not report any associated data.

- Nineteen studies met inclusion criteria (**Figure 1**); study characteristics are summarized in **Table 2**.
- Three of the 19 identified studies did not report PRO findings (Hofmeister 2010, Andorsky 2014, and Hanf 2016), leaving 16 studies that were evaluable for descriptive summarization of PRO results.
- Nine of the 19 identified studies reported on treatment regimens recommended for MCL in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas V.1.2020.[26]

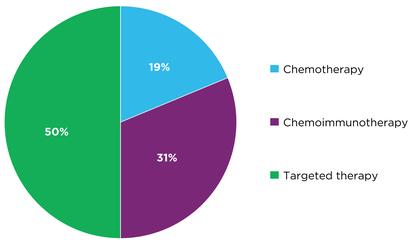
Figure 2. Types of PRO Instruments Reported (N=19)[a]



*Four studies utilized >1 PRO instrument.

- EQ-5D was the most commonly utilized QoL instrument, identified in 6 of the 19 studies (31.5%), followed by FACT-Lymphoma (Lym) and EORTC QLQ-C30 (5/19, 26.3% each; **Figure 2**).
- Four studies utilized more than one PRO instrument:
  - Hofmeister 2010: CES-D, BFI, and FACT-G
  - Hess 2017: FACT-Lym and EQ-5D-5L
  - Witzens-Harig 2009: EORTC-QLQ-C30, EQ-5D, and EQ-5D-VAS
  - Hanf 2016: SF-36, EQ-5D, and FACT-Lym

Figure 3. Categories of Treatment Regimens With PRO Results (N=16)[a]

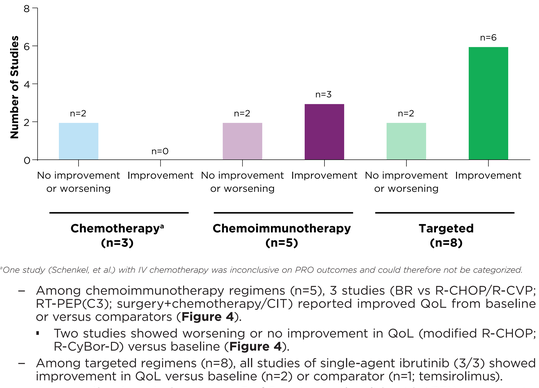


Three of the 19 identified studies were excluded from this analysis as they reported a PRO instrument in their methodology but did not present PRO data (Hofmeister 2010, Andorsky 2014, and Hanf 2016).

- Targeted therapies were the most studied regimens (n=8; **Figure 3**).

PRO Outcomes

Figure 4. Summary of PRO Findings in Studies With PRO Results



One study (Schenkel, et al.) with IV chemotherapy was inconclusive on PRO outcomes and could therefore not be categorized.

  - Among chemoimmunotherapy regimens (n=5), 3 studies (BR vs R-CHOP/R-CVP; RT-PEP(C3); surgery+chemotherapy/CIT) reported improved QoL from baseline or versus comparators (**Figure 4**).
    - Two studies showed worsening or no improvement in QoL (modified R-CHOP; R-CyBor-D) versus baseline (**Figure 4**).
  - Among targeted regimens (n=8), all studies of single-agent ibrutinib (3/3) showed improvement in QoL versus baseline (n=2) or comparator (n=1; temsirolimus).
  - Among other targeted regimens, 3 of 5 regimens (lenalidomide+RTX; enzastaurin; lenalidomide vs single-agent investigator's choice) reported improved QoL versus baseline or comparators.
    - No improvement in QoL was observed in 2 studies (rituximab maintenance versus observation; radioimmunotherapy with 90Y-ibritumomab tiuxetan).
  - Among the 16 studies that reported PRO findings, 8 studies included treatment regimens recommended for MCL by the NCCN Guidelines.[26] Of those 8 studies, 6 showed improvement in QoL (BR; CIT (R-CHOP); ibrutinib; lenalidomide+RTX) versus baseline or comparators.

LIMITATIONS

- There is a lack of standardization for gray literature search methods, resulting in potential omission of relevant sources.
- This systematic literature search was a targeted, rather than comprehensive, review.
- Medline and Embase databases are not always able to capture congress-related publications, which limited our ability to review full posters/oral presentation content.
- Heterogeneity in study designs and study populations was not adjusted for in this literature review.
- Differences in quality of evidence generated by studies identified in this literature review may potentially lead to mismatched outcome comparisons between clinical studies and real-world data.

CONCLUSIONS

- EQ-5D and EORTC QLQ-C30 were the most commonly utilized tool for evaluating PROs in patients with MCL.
- Three of 5 chemoimmunotherapy regimens were reported to result in QoL improvements.
- Three of 8 studies of targeted regimens reported on single-agent ibrutinib, which showed QoL improvement versus baseline or comparator in all 3 studies.
- Given the changing treatment landscape, future studies should continue evaluating PROs to improve the quality of care for patients with MCL.

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DISCLOSURES

KM: employment with Diplomat Specialty Pharmacy; travel expenses from Pharmacyclics LLC, an AbbVie Company, and PRA Health; other relationship(s) with Pharmacyclics LLC, an AbbVie Company; **SC & JN:** employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie; **DA:** previous employment with Eli Lilly and Company, and employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie and Eli Lilly and Company. **RI:** employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie; patents, royalties, or other intellectual property with Express Scripts.

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