Prognostic value of CD20 antigen mediated immune checkpoint inhibition in patients with acute or chronic lymphocytic leukemia

A protocol for systematic review

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Abstract
Background: The addition of rituximab to standard chemotherapy has been shown to improve response rates in patients with acute or chronic lymphocytic leukemia. However, the prognostic factors associated with progression-free survival in rituximab treated patients with lymphocytic leukemias remains unclear. We will perform a comprehensive systematic review and meta-analysis on available data on prognostic factors associated with the clinical outcomes of patients with acute and chronic lymphocytic leukemia.

Methods and analysis: This protocol for a systematic review and meta-analysis of prognostic factors has been prepared following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 guidelines. Electronic databases will be searched using keywords related to the objectives of this review. This systematic review and meta-analysis will include published randomized clinical trials, observational, prospective, and retrospective comparative cohorts. Two reviewers (ZAM and SAM) will independently screen studies, with a third reviewer consulted in cases of disagreements using a predefined data extraction sheet. Moreover, the risk of bias and the quality of evidence were independently assessed using the quality in prognostic studies tool (QUIPS). The I2 and chi squared statistical tests will be used to analyze statistical heterogeneity across studies. An I2 values of > 50% will be considered substantial. All data analysis will be performed using STATA 16.0 (StataCorp LP, TX, USA). The outcomes examined will be progression-free and overall survival.

Ethics and dissemination: No ethical approval will be required and the findings of this meta-analysis will be published in a peer-reviewed journal.

Systematic review registration: International prospective Register of Systematic Reviews (PROSPERO) number: CRD42021218997.

Abbreviations: CLL = chronic lymphocytic leukemia; R-chemo = rituximab plus chemotherapy.

Keywords: acute lymphoblastic leukemia, chemoimmunotherapy, chronic lymphocytic leukemia, rituximab

Key Points
- This systematic review and meta-analysis will be the first to synthesise the prognostic factors associated with Rituximab and the effectiveness of rituximab-based therapy in patients with acute and chronic lymphocytic leukemia.
- To our knowledge, this systematic review will offer a robust assessment of the evidence and quality of clinical and cell-based traditional and novel prognostic factors.
- The various disease stage and the severity of the disease in CLL/ALL patients included in the studies will be one of the limitations of this systematic review and meta-analysis.

1. Introduction
Chronic lymphocytic leukemia (CLL) is characterized by progressive proliferation and accumulation of functionally incompetent lymphocytes in the peripheral blood, bone marrow, lymph nodes, and spleen.⁴ CLL is predominantly due to
profound defects in B lymphocytes and is also characterized by T-cell exhaustion,[3] whereas acute lymphocytic leukemia (ALL) involves aggressive accumulation of blasts in the bone marrow and has been the primary cause of cancer-related mortalities in children and adolescents.[4,5] CLL is considerably more severe in adult patients over the age of 65 years[4] and men are disproportionately affected, with a higher incidence than women.[6–9] This can be attributed to gender-specific hormonal differences or the variance in IGVH gene usage and mutational status.[10]

Several clinical and genetic-based prognostic markers have been established. In fact, the CLL international prognostic index (CLL-IPI) includes validated clinical, genetic, and laboratory features in the prognostication of patients with CLL.[11] The incidence of CLL varies widely across geographic locations, with a high distribution of chronic lymphocytic leukemia in most European and North American countries.[9] In comparison, ALL affects, with a higher incidence than women.[6–9] This can be attributed to gender-specific hormonal differences or the variance in IGVH gene usage and mutational status.[10]

1.1. Research question
Does combining rituximab with standard chemotherapy improve progression-free survival of patients with CLL?

1.2. Objectives
To assess progression-free and overall survival in patients with CLL on rituximab or immunochemotherapy containing rituximab. Furthermore, to determine novel prognostic factors (cell-based proteins: CD38, ZAP70, CD49D; Serology: β2M, thymidine kinase, lactate dehydrogenase, Interleukin 8) associated with poor patient outcomes.

2. Methods
This protocol for a systematic review and meta-analysis has been prepared in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 (PRISMA-P) guidelines. The protocol was registered with the online PROSPERO registry (CRD42021218997).

2.1. Study design
In this review, we will include randomized control trials, prospective and retrospective comparative cohorts.

2.1.1. Inclusion criteria. Only primary studies assessing the prognosis (progression-free and overall survival) of patients with CLL on rituximab-based therapy will be included. The search will be restricted to full-text human studies written in English.

2.1.2. Exclusion criteria. Cross-sectional and case-control studies will be excluded. In addition, review articles, letters, and editorials will be excluded.

2.2. Population
Patients with CLL on rituximab-based therapy, will be included.

2.3. Index prognostic factor
We will consider the predictive factors included in the widely used CLL International Prognostic Index (CLL-IPI).[2,3] We will also consider the predictive factors used in the German CLL Study Group (GCLLSG),[24] the MD Anderson Cancer Center (MDACC) nomogram[25,26] predictive models.

2.4. Comparators
The comparators will include patients receiving standard therapy or usual care.

2.5. Outcomes
The primary outcome will be the overall 5-year overall survival, and the secondary outcome will include 2- to 4-year progression-free survival.

2.6. Timing and setting
The predictive information and measurements at diagnosis and initiation of treatment will be considered. Moreover, we will include studies reporting on inpatient and outpatient cohorts.

2.6.1. Search strategy and study selection. The search strategy will be developed using medical subject headings (MeSH) for MEDLINE, and this will be adapted to EBSCOhost search headings terms. We will search the databases from inception to February 28, 2021. The search strategy will consist of search terms that include chronic lymphocytic leukemia, acute lymphoblastic leukemia, rituximab (Supplementary file 1, http:// links.lww.com/MD/G614).
2.7. Data management
2.7.1. Data collection process. The reviewers (ZAM and SAM) will develop a structured data extraction form that will be used in the data extraction process. Mendeley referencing manager will be used in this systematic review. The screening of the articles will be independently assessed by 2 reviewers (ZAM and SAM).

2.7.2. Data items. The 2 reviewers (ZAM and SAM) will extract data items using the data items defined in the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies for prognostic factors (CHARMS-PF).[28] This will include the following information: source of data, participant description, the study dates, sample size, predicted outcome including outcome measures (hazards, odds ratio), candidate predictors, handling of missing data, modeling method, and model performance.

2.7.3. Data simplification. Studies will be grouped according to the type of lymphocytic leukemia (CLL or ALL). In addition, studies will be grouped based on the gender ratio, age of participants and chemotherapy regimen used (e.g., fludarabine, cyclophosphamide, ibritinib), duration of intervention and follow-up.

2.7.4. Risk of bias in individual studies. To assess the potential risk of bias in the included studies the quality in prognostic studies (QUIPS) tool will be used.[29] Two authors (ZAM and SAM) will independently assess the included studies based on the 6 domains of the tool. In a case of disagreements, a third reviewer (BBN) will be consulted for arbitration.

2.8. Data synthesis
A summary of findings table (SoF) will be used to provide a synthesis of the main outcomes of included studies. Furthermore, if the included studies are homogeneous in terms of the type of lymphocytic leukemia treated, therapy used, and participant characteristics, data will be analyzed using a fixed-effects model. All data analysis will be performed using R statistical software (The R Foundation for statistical computing, Vienna, Austria). The I² and chi-squared statistical tests will be used to analyze statistical heterogeneity between studies.[30,31] An I² value of >50% will be considered substantial heterogeneity.[32]

2.9. Subgroup analysis
To explore the sources of heterogeneity within the included studies, we will perform a subgroup analysis based on the study-level characteristics, including the risk of bias of the included studies, geographic location, intervention type (rituximab plus chemotherapy [R-Chemo] and chemotherapy regimens). Lastly, the reported measure of progression-free and overall survival will also be considered in the subgroup analysis.

2.10. Confirmation of predictive factors
The prognostic factors will be confirmed based on the consistency of the overall direction of the effect across the included studies. In addition, adjusted effect sizes that remain statistically significant (P < .05) after adjusting for covariates and multivariate analysis will be considered as confirmed.

2.10.1. Quality assessment of the cumulative evidence. The quality and strength of the evidence of the confirmed prognostic factors will be evaluated by 2 independent reviewers (ZAM, SAM) using the Grading of Recommendations Assessment Development and Evaluation approach (GRADE).[33]

2.11. Patient and public involvement
There is no patient or public involvement in the process of conducting this study.

3. Discussion
Rituximab-based therapy has demonstrated therapeutic benefits in the treatment of patients with lymphocytic leukemia. This systematic review and meta-analysis of prognostic factors will provide a comprehensive synthesis of studies reporting on progression-free survival in patients with CLL on a rituximab-based regimen compared with standard chemotherapy. Moreover, this review will provide a synthesis of traditional and novel cell-based prognostic factors. To our knowledge, this will be the first meta-analysis to evaluate the efficacy of R-chemo and predictive factors associated with progression-free survival in patients with ALL and CLL compared with chemotherapy alone. Findings from this study will provide insight into the prognostic factors in patients with CLL following R-chemo and will assist in the patient management and prognostication.

Author contributions
Zekhethelo A. Mkhwanazi, Snenhlanhla A. Mfusi, Bongani B. Nkambule conceptualized, designed the study, and drafted the protocol. Zekhethelo A. Mkhwanazi and Bongani B. Nkambule wrote the first draft. All authors approved the final manuscript. Bongani B. Nkambule provided supervision and is the guarantor of the review.

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References
[1] Rodrigues CA, Gonçalves MV, Ikoma MRV, et al. Diagnosis and treatment of chronic lymphocytic leukemia: recommendations from the Brazilian Group of Chronic Lymphocytic Leukemia. Rev Bras Hematol Hemoter 2016;38:346–57.
[2] Xiao X, Ye X, Xu C, Huang J. Successful alternative treatment for relapsed adult acute lymphoblastic leukemia with dendritic cells-cytokine-induced killer cells combined with a rituximab-based regimen. Onco Targets Ther 2018;11:7555–8.
[3] Riches JC, Davies JK, Mclanahan F, et al. T cells from CLL patients exhibit features of T-cell exhaustion but retain capacity for cytokine production. Blood 2013;121:1612–21.
[4] Heatley SL, Sadras T, Kok CH, et al. High prevalence of relapse in children with Philadelphia-like acute lymphoblastic leukemia despite risk-adapted treatment. Haematologica 2017;102:e490–3.
[5] Gribben JG. Chronic lymphocytic leukemia: planning for an aging population. Expert Rev Anticancer Ther 2010;10:1389–94.
[6] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
[7] Catovsky D, Fook J, Richards S. Prognostic factors in chronic lymphocytic leukaemia: the importance of age, sex and response to...
treatment in survival A report from the MRC CLL 1 trial. M.R.C. Working party on Leukemia in adults. Br J Haematol 1989;72:141–9.

[8] Mandelli F, de Rossi G, Mancini P, et al. Prognosis in chronic lymphocytic leukemia: a retrospective multicentric study from the GIMEMA group. J Clin Oncol 1987;5:398–406.

[9] Miranda-Filho A, Piéters M, Ferlay J, Soerjomataram I, Monnereau A, Bray F. Epidemiological patterns of leukaemia in 184 countries: a population-based study. Lancet Haematol 2018;5:e14–24.

[10] Catovsky D, Wade R, Else M. The clinical significance of patients’ sex in chronic lymphocytic leukemia. Haematologica 2014;99:1088–94.

[11] Bergmann MA, Eichhorst BF, Busch R, et al. Prospective evaluation of prognostic parameters in early stage chronic lymphocytic leukemia (CLL): results of the CLL1-protocol of the German CLL Study Group (GCLLSG). Am Soc Hematol 2007;110:625.

[12] Parkin DM, Muir CS, Whelan SL, et al. Cancer Incidence in Five Continents, Vol. 6. Lyon: IARC Scientific Publications; 1992. 120.

[13] Shenoy PJ, Malik N, Sinha R, et al. Racial differences in the presentation and outcomes of chronic lymphocytic leukemia and variants in the United States. Clin Lymphoma Myeloma Leuk 2011;11:498–506.

[14] Pui C-H, Boyett JM, Hancock ML, et al. Outcome of treatment for childhood cancer in Black as compared with white children. The St Jude children’s research hospital 1962 through 1992. JAMA 1995;273:633–7.

[15] Bhatia S, Sather HN, Heerema NA, Trigg ME, Gaynon PS, Robison LL. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. Blood 2002;100:1957–64.

[16] Pollock BH, DeBaun MR, Camitta BM, et al. Racial differences in the survival of childhood B-precursor acute lymphoblastic leukemia: a paediatric oncology group study. J Clin Oncol 2000;18:813–23.

[17] Kadan-Lottick NS, Ness KK, Bhatia S, Gurney JG. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. JAMA 2003;290:2008–14.

[18] Liu L, Krailo M, Reaman GH, Bernstein L. Childhood cancer patients’ access to cooperative group cancer programs: a population-based study. Cancer 2003;97:1339–45.

[19] Goggins WB, Lo FFK. Racial and ethnic disparities in survival of US children with acute lymphoblastic leukemia: evidence from the SEER database 1988-2008. Cancer Causes Control 2012;23:737–43.