Effectiveness of dose-intensified salvage regimens versus standard-dose chemotherapy for progression-free survival in early progressed follicular lymphoma before autologous stem cell transplantation: a systematic review protocol

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ABSTRACT

Objective: This review will evaluate the effectiveness of dose-intensified versus standard-dose salvage regimens on progression-free survival in early progressed follicular lymphoma before high-dose chemotherapy and autologous stem cell transplantation.

Introduction: Despite the substantial advances in the management of follicular lymphoma, approximately 20% of patients experience progression of the disease within 2 years of induction therapy. These patients have worse outcomes, and autologous stem cell transplantation has been shown to improve outcomes in this context. Little is known about the optimal salvage regimen.

Inclusion criteria: Studies must include patients ≥ 18 years old with early progressed follicular lymphoma who were submitted to autologous stem cell transplantation in subsequent remission. Clinical trials and observational studies will be included.

Methods: The search strategy will be carried out in MEDLINE (PubMed), Embase (Periódicos CAPES), Scopus, Web of Science, LiLACS, and the Cochrane Library. No date or language restrictions will be imposed. The recommended JBI approach to critical appraisal, study selection, data extraction, and data synthesis will be used. Studies should score at least 50% in accordance with the critical appraisal tool. Data will be pooled whenever possible using the random effects model. Heterogeneity will be assessed using the standard χ^2 and I^2 tests. A funnel plot will be generated to assess publication bias if there are 10 or more studies included in the meta-analysis. The GRADE approach will be used to rate certainty of evidence.

Review registration: PROSPERO CRD42022373345

Keywords: bone marrow transplantation; early relapse; follicular lymphoma; POD24; salvage chemotherapy

JBI Evid Synth 2024; 22(9):1850–1856.

Introduction

Follicular lymphoma (FL) is an indolent non-Hodgkin's lymphoma with a heterogeneous nature. It ranks as the second most prevalent non-Hodgkin's lymphoma in the United States and Europe, and affects around 15,000 patients annually in the United States.[1] Despite significant advancements in FL management over recent decades through the addition of rituximab to induction chemotherapy,[2–5] approximately 20% of patients experience progression of disease (POD) within 2 years of treatment.[3,4,6] Time to progression has emerged as a prominent prognostic factor among various risk factors, consistently influencing outcomes, even when patients undergo rituximab maintenance as observed in the PRIMA trial.[6] To identify a sub-group with worse outcomes following diagnosis and rituximab-based

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The authors declare no conflicts of interest.

DOI: 10.11124/JBIES-23-00231

treatment, Casulo *et al.* proposed the term "POD24," referring to those patients who experienced POD within 24 months of induction chemotherapy.[7] This sub-group exhibited a 5-year overall survival of 50%, compared with 90% in the non-POD24 group.[7] Moreover, transformation to a histologically aggressive lymphoma has been observed in approximately 75% of these patients upon relapse, leading to deteriorating outcomes and survival.[8]

Although new treatments for FL have been suggested for a second-line approach, there remains a gap in the availability of innovative therapies. Considering its effectiveness in treating relapsed indolent and aggressive lymphomas, salvage chemotherapy followed by high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) consolidation has been proposed as an alternative therapeutic option in this context. A study by Casulo *et al.* analyzed data from patients registered with the Center for International Blood and Marrow Transplant Research (CIBMTR) and the National LymphoCare Study (NLCS).[9] The study included patients diagnosed with FL who had experienced early therapy failure, characterized by either a failure to achieve at least a partial response after induction chemoimmunotherapy or relapse within 2 years of induction chemoimmunotherapy. Two distinct groups were identified: the non-ASCT cohort obtained from the NLCS, and the ASCT group derived from the CIBMTR registry. Patients who were diagnosed with histologic transformation at the time of relapse were excluded from the analysis. The authors of the study demonstrated an improved 5-year overall survival rate for patients classified as primary refractory or early relapsed, who underwent ASCT within 1 year of treatment failure (73% versus 60%, $P = 0.05$).[9] However, among the various salvage chemotherapies used before HDC and ASCT, no published consensus has been found regarding the therapy that would yield the best outcomes.

A preliminary search of MEDLINE, PROSPERO, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted, and no current or in-progress systematic reviews on the topic were identified. This study protocol is registered in PROSPERO (CRD 42022373345).

Review question

What is the effectiveness of dose-intensified versus standard-dose salvage regimens on progression-free survival in early relapsed FL patients before submission to HDC and ASCT?

Inclusion criteria

Participants

This review will consider studies that include patients ≥ 18 years old, diagnosed with FL refractory to or experiencing POD24 after induction chemotherapy who are eligible for HDC and ASCT as consolidation therapy. Patients will be considered refractory or early relapsed if they meet the following criteria: failure to achieve a minimum of 50% reduction in the sum of the product of the greatest diameters of the 3 largest lesions as determined by computed tomography (CT) scan or positron emission tomography (PET)/CT, following induction therapy; or evidence of new lymph node biopsy of FL relapse without aggressive transformation (motivated by lymph node enlargement, persistence of B symptoms, or increased uptake on PET/CT after initial response).[10,11] Studies on participants with aggressive transformation of indolent lymphoma at relapse, HIV/AIDS infection, estimated glomerular filtration rate < 15mL/min/1.73m² body surface area, or those undergoing renal replacement therapy in their analyses will be excluded.

Interventions

This review will consider studies that evaluate dose-intensified second-line cytoreductive regimens in the presence or absence of anti-CD20 antibodies on day (D) 1, such as:

- ICE: ifosfamide 5000 mg/m² intravenous (IV) D2, carboplatin area under the curve (cap dose at 800 mg) IV D2, etoposide 100 mg/m² IV D1 to D3, on a 21-day cycle for 3 cycles
- DHAP: cisplatin 100 mg/m² IV over 24 hours on D1, cytarabine 2000 mg/m² IV twice a day 12 hours apart D2, and dexamethasone 40 mg orally (PO) once a day from D1 to D4, on a 21- to 28-day cycle for 2 to 4 cycles
- ESHAP: methylprednisolone sodium succinate 500 mg IV D1 to D5, cisplatin 25 mg/m² IV D1 to D4, etoposide 40mg/m² IV D1 to D4, cytarabine 2000 mg/m² IV D5, on a 21- to 28-day cycle for 3 to 6 cycles
- GDP: dexamethasone 40 mg PO once daily D1 to D4, gemcitabine 1000 mg/m² IV D1 to D8, cisplatin 75 mg/m² IV D1 on a 21-day cycle for 2 to 3 cycles.

All regimens must be followed by HDC and ASCT as a consolidative approach after the cytoreductive regimen.

Comparators

This review will consider studies that compare the intervention to standard-dose second-line cytoreductive regimens in the presence or absence of anti-CD20 antibodies, such as:

- CHOP: prednisolone 100 mg PO D1 to D5, doxorubicin 50 mg/m² IV D1, vincristine 1.4 mg/m² (cap dose at 2 mg) IV D1, cyclophosphamide 750 mg/m² IV D1, on a 21-day cycle for 6 to 8 cycles
- CVP: prednisolone 40 mg/m² PO D1 to D5, cyclophosphamide 750 mg/m² IV D1, vincristine 1.4 mg/m² (cap dose at 2 mg) IV D1, on a 21-day cycle for 6 to 8 cycles
- Bendamustine 90 mg/m² IV D1 and D2, on a 28-day cycle for 6 cycles.

All regimens must be followed by HDC and ASCT as a consolidative approach after the cytoreductive regimen.

Outcomes

This review will consider studies that include the following outcomes:

- progression-free survival, termed as time from diagnosis to death by any cause or disease progression, defined as new lymph node biopsy showing FL relapse without aggressive transformations (motivated by lymph node enlargement, persistence of B symptoms, or increased uptake on PET/CT) after initial response or failure in achieving at least 25% reduction on the sum of the product of greatest diameters of the 3 largest lesions,[10] identified by CT scan or PET/CT after second-line cytoreductive regimen
- overall survival assessed and defined as the time from disease diagnosis to death from any cause
- partial response evaluated and defined as achieving a minimum of 50% reduction in the sum of the product of the 3 largest lesions' greatest diameters,[10] as identified by CT scan or PET/CT, and/or obtaining a score of 4 or 5 on a PET 5-point scale with reduced uptake compared with baseline and no new lesions after salvage regimen
- complete response, defined as disappearance of any previously measured or non-measured lesions and no new lesions, and a score 1, 2, or 3 with or without a residual mass on a PET/CT 5-point scale and no evidence of fluorodeoxyglucose-avid disease in the bone marrow.

Types of studies

This review will consider randomized controlled trials; non-randomized controlled trials; analytical observational studies, including prospective and retrospective cohorts; case-control studies; and analytical cross-sectional studies. Case reports, case series, review articles, and conference presentations will be excluded. This limitation on eligible study types is intended to ensure less heterogeneity in the results.

Methods

The proposed review will adhere to the JBI methodology for systematic reviews of effectiveness.[12]

Search strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of MEDLINE (PubMed), Scopus (Periódicos CAPES), LiLACS, and the Cochrane Library was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles, were used to develop a full search strategy for MEDLINE (PubMed; see Appendix I). The reference lists of all studies selected for critical appraisal will be screened for additional studies.

No limitations regarding study language will be imposed. Translations in English, Spanish, Portuguese, and French will be handled by the authors. Any potentially eligible paper written in another language will be sent to a translator provided by an affiliated institution of the reviewers. Studies published from database inception to the present will be included.

The databases to be searched will include MEDLINE (PubMed), Embase (Periódicos CAPES), Scopus (Periódicos CAPES), Web of Science (Periódicos CAPES), LiLACS, and Cochrane Library. The search strategy will be adapted to each database. Authors will be contacted if additional data are needed. Sources of unpublished studies and gray literature will include ClinicalTrials.gov, Google Scholar, ScienceDirect, Networked Digital Library of Theses and Dissertations, DART-Europe E-theses portal, dissertation catalogs, and CAPES theses banks.

Study selection

All identified citations will be collated and uploaded into Mendeley v. 1.19.8 (Mendeley Ltd, Elsevier, Netherlands) and duplicates removed. Following a pilot test, titles and abstracts will be screened by 2 independent reviewers against the inclusion criteria. Potentially relevant studies will be retrieved in full, and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia).[13] The full text of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or with a third reviewer. The results of the search and study selection and inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[14]

Assessment of methodological quality

Eligible studies will be critically appraised by 2 independent reviewers at the study level for methodological quality using standardized critical appraisal instruments from JBI for experimental, quasi-experimental, and observational studies.[12] Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The results of critical appraisal will be reported in a table with an accompanying narrative.

Following critical appraisal, studies that do not meet a certain quality threshold will be excluded. This decision will be based on achieving a score of at least 50%, in accordance with the JBI quality assessment instrument, adapted to the specific form related to the study design. The cut-off threshold choice will be arbitrary, after assessing other systematic reviews from the health science literature and after conducting the pilot search test for methodological evaluation.

Data extraction

Data will be extracted by 2 independent reviewers using a table designed by the authors in Microsoft Excel v. 16.0.15028.20160 (Redmond, Washington, USA; Appendix II). The data extracted will include first author and year of publication, study design, number of participants with FL, median population age, staging (Lugano or modified Ann Arbor) $\geq$ IIIa,[11] refractoriness (%), number of previous lines of chemoimmunotherapy, median overall survival (months), median progression-free survival (months), complete response rate (%), and partial response rate (%). Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required. We will contact authors twice over a 30-day period via email. Authors who do not respond will have their papers excluded from the analysis.

Data synthesis

Studies will, when possible, be pooled with statistical meta-analysis using JBI SUMARI.[13] Statistical analyses will be performed using the random effects model due to high clinical and methodological variability among studies published on the topic.[15] Heterogeneity will be assessed statistically using the standard χ^2 and I^2 tests. The P-value < 0.05 in the χ^2 test presumes the presence of heterogeneity. The inconsistency calculation (I^2) will be done to measure the depth of heterogeneity among the studies, as follows: 0%–40%, 30%–60%, 50%–90%, 75%–100% indicates major heterogeneity. Sensitivity analyses will be performed to explain the effect of systematic errors across studies, demonstrated by the heterogeneity found in the χ^2 and I^2 tests. To this end, sensitivity analyses will be carried out by excluding studies with a sample size that differs from the others, missing data, and/or baseline imbalance. If the χ^2 and I^2 tests demonstrate high heterogeneity and this is not explained by sensitivity analyses, the fixed effects models will be applied in the meta-analysis. With respect to visual analysis of the forest plot, the presence of a confidence interval overlap will indicate substantial heterogeneity. Where statistical analysis is not possible, the findings will be presented in narrative format, including tables and figures to aid in data presentation, where appropriate.

A funnel plot will be generated on janovi software v. 2.3.18 (The janovi project, Sydney, Australia) to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test,[16] Begg test,[17] Harbord test[18]) will be performed where appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach[19] for

grading the certainty of evidence will be followed and a Summary of Findings will be created using GRADEpro GDT software (McMaster University, ON, Canada). The Summary of Findings will present the following information where appropriate: absolute risks for the treatment and control; estimates of relative risk; and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication bias of the review results. The outcomes reported in the Summary of Findings will be complete response rate, partial response rate, overall survival, and progression-free survival.

Author contributions

FPM contributed to the search strategy, as well as conducting the pilot search and collecting data. JAT contributed to the search strategy. MGDGS helped collect data. All authors contributed to the writing and reviewing of the final submitted manuscript.

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Appendix I: Search strategy

MEDLINE (PubMed)
Search conducted: May 19, 2023

Search	Query	Records retrieved
#1	(("Follicular Lymphoma"[tw]) OR ("Lymphoma, Follicular" [Mesh]))	9957
#2	(("Early relapse"[tw]) OR ("Refractory"[tw]) OR ("POD24"[tw]))	158,808
#3	(("Autologous Transplantation"[tw]) OR ("Bone Marrow Transplantation"[tw]))	57,371
#4	#1 AND #2 AND #3	34
No restrictions on language or date.		

Appendix II: Draft data extraction instrument

First author, year	
Study design	
Total number of patients	men/women
Median age	years (range)
Patients stated as >IIIa according to Lugano classification scale	
Number of refractory patients	%
Number of previous chemotherapy lines	
Median overall survival	months (range)
Median progression-free survival	months (range)
Complete response rate	%
Partial response rate	%