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Prednisolone-Sparing Regimens in Combination Chemotherapy for Lymphoma: Toxicity and Response Outcomes

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ABSTRACT

Background: Corticosteroids such as prednisone and prednisolone are integral components of combination chemotherapy for Hodgkin and non-Hodgkin lymphoma, but their inclusion is associated with hyperglycemia, myopathy, opportunistic infection, and other toxicities that disproportionately affect older and frailer patients. Objective: This narrative review synthesizes published evidence on prednisolone-sparing and steroid-attenuated combination chemotherapy regimens for lymphoma, focusing on their toxicity profiles and response/survival outcomes. Methods: Primary clinical trial reports, retrospective cohort studies, and mechanistic reviews addressing corticosteroid dose modification in lymphoma chemotherapy, including R-CHOP, R-miniCHOP, dose-adjusted EPOCH-R, VEPEMB, and PVAG, were identified and synthesized thematically. Findings: Dose-attenuated regimens such as R-miniCHOP achieved 2-year overall survival of 59% in patients over 80 years old with diffuse large B-cell lymphoma, while the reduced-intensity PVAG regimen achieved a 78% complete remission rate and 66% 3-year overall survival in elderly Hodgkin lymphoma, with treatment-related mortality below 10% in both settings despite substantial grade 3-4 toxicity. Corticosteroid-attributable hyperglycemia, myopathy, and opportunistic infection persisted even in attenuated regimens, and dose modification was consistently implemented alongside parallel changes to anthracycline dose, cycle length, or antibody use, precluding isolation of the corticosteroid contribution alone. Conclusions: Prednisolone-sparing and steroid-attenuated regimens preserve meaningful anti-lymphoma activity while reducing, but not eliminating, corticosteroid-related toxicity, supporting their role in fitness- and frailty-stratified treatment algorithms for older or less fit lymphoma patients.

Keywords: *prednisolone-sparing chemotherapy; lymphoma toxicity; R-miniCHOP; corticosteroid-related adverse effects; elderly Hodgkin lymphoma treatment*

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Introduction

Corticosteroids have occupied a central position in combination chemotherapy for both Hodgkin and non-Hodgkin lymphoma since the earliest multi-agent regimens were assembled, contributing direct lympholytic activity, anti-emetic and anti-allergic support for concurrently administered cytotoxic agents, and amelioration of tumor-related B symptoms [1]. In the standard CHOP backbone (cyclophosphamide, doxorubicin, vincristine, prednisone) and its rituximab-containing derivative R-CHOP, prednisone or prednisolone is typically dosed at 40-100 mg/m2 daily for five days per 21-day cycle, a schedule validated in the pivotal trial that established rituximab-CHOP as standard first-line therapy for elderly diffuse large B-cell lymphoma (DLBCL) [2]. Yet this same corticosteroid component, while mechanistically integral to lymphoma cell kill through glucocorticoid-receptor-mediated apoptosis, is also a recognized driver of a distinctive toxicity signature that includes hyperglycemia, proximal myopathy, osteoporosis and osteonecrosis, neuropsychiatric disturbance, and opportunistic infection, effects that are disproportionately consequential in the older, frailer, and more comorbid patients who make up a growing share of the lymphoma population [3,4].

This tension between corticosteroid efficacy and corticosteroid toxicity has motivated a distinct line of clinical investigation aimed at prednisolone-sparing or steroid-attenuated combination regimens, particularly for patients aged 70, 80, or older, for whom full-dose CHOP-based therapy is often either not tolerated or associated with excessive early mortality [5,6]. Strategies pursued in this space have included straightforward dose attenuation of prednisone alongside proportional reduction of the other

cytotoxic components, as exemplified by R-miniCHOP for patients older than 80 years [5,7], substitution of prednisone with alternative agents or omission of prednisone from otherwise intensified backbones, as in the two-weekly CHOP-with-etoposide comparisons of the DSHNHL group [8], and, in classical Hodgkin lymphoma, the deliberate construction of lower-intensity, non-bleomycin regimens such as VEPEMB and PVAG that retain a corticosteroid but at reduced cumulative exposure relative to standard ABVD or BEACOPP [9,10,11].

This narrative review synthesizes the published literature on prednisolone-sparing and steroid-attenuated combination chemotherapy regimens for lymphoma, organizing the discussion around the pharmacological and clinical rationale for corticosteroid modification, the clinical trial evidence for specific steroid-sparing or steroid-reduced regimens in both Hodgkin and non-Hodgkin lymphoma, the corticosteroid-attributable toxicities that these strategies seek to mitigate, and the comparative response and survival outcomes reported across this body of work. Because corticosteroid dose modification is almost never studied as an isolated variable, the regimens reviewed here vary simultaneously in anthracycline dose, cycle length, and use of monoclonal antibody therapy, a limitation that is addressed explicitly in the discussion of outcomes below.

Rationale for Corticosteroid Modification in Lymphoma Chemotherapy Regimens

Glucocorticoids induce apoptosis in malignant and normal lymphocytes through a glucocorticoid-receptor-dependent transcriptional program that activates pro-apoptotic genes including BIM, while simultaneously repressing anti-apoptotic and inflammatory signaling, an action that is both the basis for corticosteroid inclusion in lymphoma regimens and a recognized source of variable clinical resistance when this pathway is dysregulated in malignant clones [1]. Because this pro-apoptotic mechanism operates on any glucocorticoid-receptor-expressing tissue, sustained or repeated high-dose corticosteroid exposure across multiple chemotherapy cycles produces off-target effects that extend well beyond the tumor compartment, and it is this off-target toxicity profile, not diminished anti-lymphoma activity, that has principally motivated dose-reduction strategies.

The clinical case for corticosteroid modification is strongest in older patients. A Surveillance, Epidemiology, and End Results (SEER)-Medicare population-based study of first-line treatment patterns in older Hodgkin lymphoma patients documented that advancing age and comorbidity burden are associated with both reduced use of full-intensity, anthracycline- and steroid-containing regimens and with inferior survival when treatment is curtailed altogether, underscoring that the clinical challenge is not simply whether to reduce corticosteroid and cytotoxic intensity but how to do so without sacrificing curative potential [6]. Frailty assessment tools developed specifically for older lymphoma patients have been proposed as a means of identifying, prospectively, which patients are likely to tolerate full-dose corticosteroid-containing chemotherapy and which require attenuated regimens from the outset, since chronological age alone correlates poorly with corticosteroid tolerance [12]. Contemporary "how I treat" guidance for older DLBCL patients in the frontline setting similarly frames the treatment decision explicitly around fitness-based stratification, with full-dose R-CHOP reserved for fit patients, attenuated regimens such as R-miniCHOP for intermediate-fitness patients, and further dose reduction or palliative approaches for frail patients, a framework in which the corticosteroid dose is one of several levers adjusted in parallel with anthracycline dose and cycle number [13].

A second and distinct rationale for corticosteroid modification arises from acute metabolic and infectious toxicity observed even in younger and fitter patients receiving standard-dose regimens. Retrospective analyses of patients receiving R-CHOP or dose-adjusted R-EPOCH for non-Hodgkin lymphoma have found that steroid-induced hyperglycemia is common during treatment, frequently severe enough to prompt chemotherapy dose or schedule alteration, and associated with an activation of glucose-lowering therapy that persists into subsequent cycles, findings that argue for closer attention to corticosteroid dosing and monitoring irrespective of patient age [14,4]. Corticosteroid-associated immunosuppression additionally potentiates the risk of opportunistic infection when combined with rituximab-based B-cell depletion, as demonstrated in a single-center series in which the incidence of Pneumocystis jirovecii pneumonia rose sharply among patients receiving rituximab-CHOP-14 until routine trimethoprim-sulfamethoxazole prophylaxis was instituted, a finding that has shaped supportive-care recommendations for corticosteroid-containing regimens more broadly [15]. Together, these lines of evidence establish that corticosteroid modification in lymphoma chemotherapy is motivated by both age-related pharmacokinetic vulnerability and by toxicities, metabolic and infectious, that are relevant across the age spectrum.

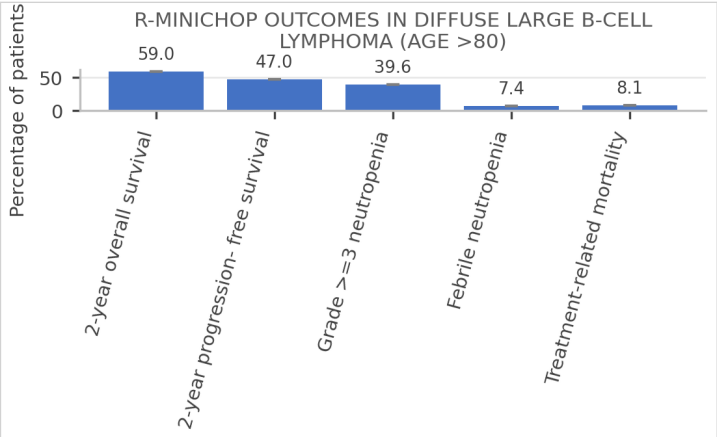
Prednisone/Prednisolone-Sparing and Dose-Attenuated Regimens: Clinical Trial Evidence

The most extensively studied prednisolone-sparing strategy in DLBCL is proportional dose attenuation of the entire CHOP backbone, exemplified by R-miniCHOP. In a multicentre, single-arm phase 2 trial enrolling 149 patients older than 80 years with DLBCL, Peyrade and colleagues administered rituximab with cyclophosphamide 400 mg/m2, doxorubicin 25 mg/m2, vincristine 1 mg (capped, not dose-per-m2), and prednisolone 40 mg/m2 for five days, roughly halving the anthracycline and cyclophosphamide doses of standard CHOP while keeping the corticosteroid schedule largely intact in relative terms; this regimen achieved a 2-year overall survival of 59% and 2-year progression-free survival of 47% in a population for whom full-dose R-CHOP had previously been considered intolerable [5]. Building on this platform, the phase 3 SENIOR trial randomized patients aged 80 years or older with DLBCL to subcutaneous R-miniCHOP with or without added lenalidomide, confirming R-miniCHOP as a feasible backbone in this population while showing that lenalidomide addition did not improve progression-free survival and increased toxicity, reinforcing that the attenuated corticosteroid-containing backbone itself, rather than added novel agents, remains the mainstay for the oldest DLBCL patients [7].

A complementary strategy has been to intensify chemotherapy schedule (dose density) while holding corticosteroid exposure constant, as tested in the DSHNHL NHL-B2 trial, which randomized elderly patients with aggressive lymphoma to two-weekly or three-weekly CHOP with or without etoposide, and in the subsequent RICOVER-60 trial, which established six cycles of two-weekly CHOP plus rituximab as superior to eight cycles for patients aged 61-80 [8]. These dose-dense approaches did not remove prednisone from the regimen but did compress its administration into a shorter overall treatment duration, thereby reducing cumulative corticosteroid exposure across the full

course of therapy even though the per-cycle dose was unchanged. In younger, fitter patients, the UK NCRI trial comparing 14-day and 21-day R-CHOP cycles found no outcome benefit to dose-dense scheduling and comparable toxicity between arms, indicating that the benefits of compressed corticosteroid and cytotoxic scheduling seen in the DSHNHL elderly trials do not necessarily generalize across age and fitness strata [16]. A structurally different attempt to modify the corticosteroid-anthracycline-alkylator balance, dose-adjusted EPOCH-R, retains prednisone but redistributes cyclophosphamide, doxorubicin, and etoposide dosing according to real-time hematologic tolerance; in the phase 3 Alliance/CALGB 50303 trial this infusional strategy produced clinical outcomes statistically indistinguishable from standard R-CHOP with higher hematologic toxicity, suggesting that pharmacodynamic dose adjustment of the non-steroid components alone is insufficient to improve on the standard corticosteroid-containing CHOP platform [17].

Two-year survival and grade 3-4 toxicity outcomes with the prednisolone-attenuated R-miniCHOP regimen in 149 patients with diffuse large B-cell lymphoma older than 80 years, the pivotal single-arm phase 2 trial establishing dose-attenuated immunochemotherapy for the oldest and least fit patients (Peyrade et al., 2011).



In classical Hodgkin lymphoma, prednisone- and prednisolone-containing regimens have been redesigned around older patients by removing bleomycin, a strategy driven primarily by pulmonary toxicity concerns but implemented alongside corticosteroid and anthracycline dose modification. The VEPEMB regimen (vinblastine, cyclophosphamide, procarbazine, prednisolone, etoposide, mitoxantrone, bleomycin at reduced dose) was developed by the Intergruppo Italiano Linfomi specifically for patients over 65 years and reported feasible toxicity in its original single-arm evaluation [9], and a subsequent randomized trial by the Fondazione Italiana Linfomi directly compared reduced-intensity VEPEMB with standard ABVD in elderly Hodgkin lymphoma patients, providing head-to-head evidence on the trade-off between regimen intensity and tolerability in this population [11]. The PVAG regimen (prednisone, vinblastine, doxorubicin, gemcitabine), developed by the German Hodgkin Study Group, substitutes gemcitabine for the more myelosuppressive and neurotoxic agents of standard combinations while retaining prednisone, and was specifically designed for elderly patients unfit for standard ABVD or BEACOPP intensity [10].

Corticosteroid-Related Toxicity: Metabolic, Infectious, Muscular, and Hematologic Effects

The toxicity profile that motivates corticosteroid-sparing regimen design has been characterized across several organ systems in the lymphoma chemotherapy literature. Hyperglycemia is among the most consistently reported acute corticosteroid-attributable toxicities: in a retrospective cohort of patients receiving R-CHOP for DLBCL, Kristjanson and colleagues found that steroid-induced hyperglycemia was common and was associated with adverse outcomes, prompting recommendations for structured glucose monitoring during corticosteroid-containing cycles [4], a finding corroborated by Lamar and colleagues, who reported that hyperglycemia during R-CHOP or dose-adjusted R-EPOCH was prevalent enough to necessitate chemotherapy alteration in a meaningful proportion of patients, independent of pre-existing diabetes status [14]. These metabolic effects are dose- and duration-dependent, providing a direct rationale for regimens, such as R-miniCHOP and PVAG, that reduce cumulative corticosteroid exposure relative to full-dose CHOP-21 or BEACOPP.

Principal prednisolone-sparing or steroid-attenuated combination chemotherapy regimens for lymphoma reviewed, with corticosteroid modification strategy and study population.

Regimen	Corticosteroid modification strategy	Study population	Key reference
R-miniCHOP	Proportional dose attenuation of full regimen including prednisolone	DLBCL, age >80 years (n=149)	Peyrade et al. 2011
R2-miniCHOP (SENIOR trial)	R-miniCHOP backbone plus/minus lenalidomide, randomized	DLBCL, age >=80 years	Oberic et al. 2021
CHOP-14 +/- etoposide, RICOVER-60	Unchanged per-cycle prednisone, compressed dose-dense schedule	Aggressive CD20+ B-cell lymphoma, age 61-80	Pfreundschuh et al. 2008
R-CHOP14 vs R-CHOP21	Unchanged prednisolone dose, dose-dense schedule comparison	DLBCL, fit adults (NCRI trial)	Cunningham et al. 2013
Dose-adjusted EPOCH-R	Prednisone retained; other cytotoxic doses individually titrated	DLBCL, Alliance/CALGB 50303	Bartlett et al. 2019
VEPEMB	Reduced-dose prednisolone within bleomycin-sparing, lower-intensity regimen	Hodgkin lymphoma, age >65 years	Levis et al. 2004; Zallio et al. 2016
PVAG	Prednisone retained; gemcitabine substituted for more toxic agents	Hodgkin lymphoma, age 60-75, unfit for ABVD/BEACOPP	Boll et al. 2011

Neuromuscular toxicity is a second well-documented corticosteroid effect relevant to lymphoma chemotherapy. Batchelor and colleagues described steroid myopathy specifically in cancer patients, a proximal, predominantly lower-extremity weakness that develops with cumulative corticosteroid exposure and can be difficult to distinguish clinically from disease-related deconditioning or chemotherapy-induced peripheral neuropathy, but which is directly attributable to glucocorticoid effects on skeletal muscle protein catabolism [3]. This toxicity is of particular concern in elderly and frail lymphoma patients, for whom preservation of functional independence during and after treatment is a key outcome, reinforcing the rationale articulated

in frailty-assessment frameworks for individualizing corticosteroid and overall regimen intensity according to baseline muscle mass and functional reserve rather than chronological age alone [12].

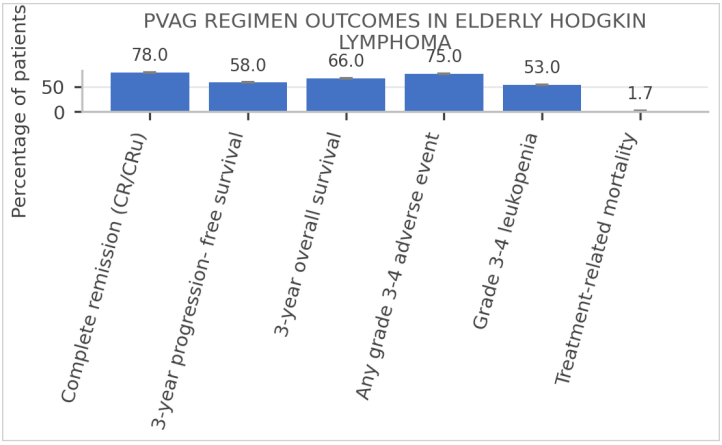
Infectious complications represent a third major corticosteroid-attributable toxicity axis, compounded in the rituximab era by concurrent B-cell depletion. Hardak and colleagues documented a marked increase in Pneumocystis jirovecii pneumonia incidence among patients receiving rituximab-CHOP-14, an effect abrogated by routine trimethoprim-sulfamethoxazole prophylaxis, directly implicating the combined immunosuppressive burden of corticosteroid and anti-CD20 therapy in this opportunistic infection risk [15]. Bartlett's review of approaches to aggressive B-cell lymphoma in less fit patients likewise emphasizes infection risk mitigation, alongside growth factor support and dose modification, as central components of safely delivering corticosteroid-containing regimens to less robust patients [18]. Finally, hematologic toxicity, principally leukopenia and neutropenia, remains prevalent even in dose-attenuated regimens: in the PVAG phase 2 trial, grade 3-4 adverse events occurred in 75% of patients and grade 3-4 leukopenia in 53%, despite the regimen's design intent of reduced intensity relative to standard Hodgkin lymphoma combinations, illustrating that corticosteroid dose reduction alone does not eliminate myelosuppressive risk contributed by the accompanying cytotoxic agents [10].

Response Rates and Survival Outcomes Across Steroid-Modified Regimens

Despite the toxicity concerns that motivate corticosteroid-sparing regimen design, the reported response and survival outcomes across these regimens indicate that meaningful anti-lymphoma activity is preserved when dose attenuation is applied thoughtfully alongside, rather than instead of, appropriate patient selection. In the R-miniCHOP trial for DLBCL patients older than 80 years, 2-year overall survival reached 59% and 2-year progression-free survival 47%, with grade 3 or higher neutropenia occurring in approximately 40% of the 149 enrolled patients, febrile neutropenia in roughly 7%, and treatment-related mortality in about 8%, an outcome regarded at the time of publication as a substantial improvement over historical outcomes with either full-dose R-CHOP or purely palliative management in this very elderly population [5]. The subsequent SENIOR trial confirmed the R-miniCHOP backbone's feasibility in a randomized setting, with the lenalidomide-containing experimental arm failing to improve on this benchmark and instead adding toxicity without a progression-free survival benefit [7].

In Hodgkin lymphoma, the PVAG regimen achieved a complete remission or unconfirmed complete remission rate of 78% among 59 patients aged 60-75 years with early unfavorable or advanced-stage disease, with 3-year progression-free survival of 58% and 3-year overall survival of 66%; treatment-related mortality was low at approximately 2%, despite a 75% incidence of any grade 3-4 adverse event, indicating that high response rates and durable disease control are achievable even when overall regimen intensity, including cumulative corticosteroid, anthracycline, and alkylator exposure, is substantially reduced relative to standard ABVD or escalated BEACOPP [10]. The VEPEMB regimen produced broadly comparable feasibility in its original single-arm evaluation in the Intergruppo Italiano Linfomi cohort [9], and the head-to-head randomized comparison with standard ABVD in elderly patients provided direct evidence on the relative efficacy-toxicity trade-off between a lower-intensity, prednisolone-containing regimen and the conventional bleomycin-containing standard [11].

Response, survival, and grade 3-4 toxicity outcomes with the reduced-intensity, prednisone-containing PVAG regimen (prednisone, vinblastine, doxorubicin, gemcitabine) in 59 elderly patients with early unfavorable or advanced-stage Hodgkin lymphoma, from the German Hodgkin Study Group phase 2 trial (Boll et al., 2011).



For non-Hodgkin lymphoma patients whose fitness permits standard-intensity therapy, the corticosteroid-containing R-CHOP backbone established by Coiffier and colleagues, and subsequently intensified through dose-dense scheduling in the DSHNHL NHL-B2 and RICOVER-60 trials, remains associated with superior outcomes relative to chemotherapy without rituximab or with reduced cycle number, indicating that corticosteroid and cytotoxic dose reduction below the standard R-CHOP benchmark should be reserved for patients in whom fitness, frailty, or comorbidity genuinely precludes full-intensity therapy rather than applied indiscriminately [2,8]. This principle is echoed in dose-adjusted EPOCH-R, where redistributing non-steroid cytotoxic dosing without altering the corticosteroid schedule failed to improve on standard R-CHOP outcomes while increasing toxicity, reinforcing that the corticosteroid component of these regimens should not be viewed in isolation from the anthracycline, alkylator, and antibody components with which its dose is co-determined in trial design [17]. Contemporary frontline treatment frameworks for older DLBCL patients synthesize this evidence into fitness-stratified algorithms in which the degree of corticosteroid and overall regimen attenuation is calibrated to an individual patient's comorbidity burden and geriatric assessment findings rather than to age or diagnosis alone [13,12].

Conclusion

The literature reviewed here demonstrates that corticosteroid-sparing and corticosteroid-attenuated combination chemotherapy regimens for lymphoma occupy a well-defined and evidence-supported niche, principally among older and less fit patients for whom full-dose, prednisone-containing CHOP-based or ABVD/BEACOPP-based therapy carries excessive toxicity risk. Regimens such as R-miniCHOP, PVAG, and VEPEMB achieve response rates and survival outcomes that, while generally inferior to those reported with full-intensity therapy in fit patients, represent substantial improvements over historical outcomes in populations previously considered too frail for curative-intent treatment, with treatment-related mortality maintained in the single-digit percentage range across these regimens. At the same time, corticosteroid-attributable toxicities,

hyperglycemia, myopathy, opportunistic infection, and hematologic suppression, remain measurable even in dose-attenuated regimens, indicating that corticosteroid dose reduction mitigates but does not eliminate this toxicity signature, and that supportive-care measures such as glucose monitoring and Pneumocystis prophylaxis retain importance regardless of corticosteroid dose. Because corticosteroid modification in the reviewed trials was consistently implemented alongside parallel changes to anthracycline dose, cycle length, or antibody use, the specific contribution of the prednisolone dose reduction itself to either efficacy or toxicity outcomes cannot be isolated from these composite regimen designs, a limitation that argues for continued incorporation of objective frailty and geriatric assessment tools to guide individualized corticosteroid and overall regimen intensity in future lymphoma trials.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Matthias Meyer conceived the review, conducted the literature search, and drafted the manuscript. Antoine Perrin contributed to the literature screening and pharmacological framing and critically revised the manuscript for important intellectual content. Rasmus Kask contributed additional clinical pharmacology context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published clinical trial and observational literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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