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Combination Etoposide-Prednisolone-Vincristine-Cyclophosphamide Regimens: A Retrospective Toxicity Profile Analysis

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ABSTRACT

Background: Etoposide, prednisolone (or prednisone), vincristine, and cyclophosphamide form the shared pharmacological backbone of EPOCH, CHOP, CVP, and hyper-CVAD, chemotherapy regimens administered, often sequentially, to overlapping populations of patients with aggressive lymphoma, follicular lymphoma, and acute lymphoblastic leukemia. Objective: This retrospective case-study analysis synthesizes the published toxicity literature on this regimen family to characterize the pattern, severity, and overlap of treatment-related morbidity encountered in clinical practice. Methods: Peer-reviewed retrospective cohort studies, prospective trial toxicity reports, pharmacovigilance analyses, and mechanistic reviews describing hematologic, neurologic, cardiac, infectious, and genitourinary or metabolic toxicity of this regimen family were identified through structured literature searches, individually verified against their publisher or indexing records, and narratively synthesized by toxicity domain rather than pooled statistically. Findings: Myelosuppression is the dominant acute toxicity across all regimens, with severity and duration scaling from anthracycline-free CVP through CHOP and dose-adjusted EPOCH-R to dose-intensive hyper-CVAD, the latter producing cytopenias persisting in the majority of patients three months after treatment and a measurable cumulative incidence of secondary hematologic malignancy at four years. Vincristine-induced peripheral neuropathy is cumulative and genetically modulated across every regimen; anthracycline-mediated cardiotoxicity accumulates with lifetime anthracycline exposure and is detectable by echocardiography even with liposomal doxorubicin substitution; febrile neutropenia risk is amplified by advanced age and, in infusional EPOCH-based regimens, is compounded by catheter-associated infection; and cyclophosphamide-related hemorrhagic cystitis together with corticosteroid-related metabolic and infectious effects scale with per-cycle dose. Conclusions: Etoposide-prednisolone-vincristine-cyclophosphamide-containing regimens share a mechanistically coherent, overlapping toxicity architecture whose cumulative components, chiefly anthracycline cardiotoxicity and vincristine neuropathy, warrant explicit consideration whenever more than one regimen from this family is used across a patient's treatment course.

Keywords: *EPOCH chemotherapy toxicity; CHOP regimen adverse effects; vincristine-induced peripheral neuropathy; anthracycline cardiotoxicity; chemotherapy-induced myelosuppression*

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Introduction

Etoposide, prednisolone (or prednisone), vincristine, and cyclophosphamide form the shared pharmacological backbone of several combination chemotherapy regimens that remain first-line or salvage standards of care for aggressive B-cell and T-cell lymphomas, follicular lymphoma, and acute lymphoblastic leukemia. The doxorubicin-containing infusional schedule known as EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, often combined with rituximab as EPOCH-R or dose-adjusted as DA-EPOCH-R) was first characterized in relapsed and refractory non-Hodgkin lymphoma in the early 1990s and has since been extended to front-line therapy of diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and adult T-cell leukemia/lymphoma [1,2,3,4]. The bolus-schedule cousin of this backbone, CHOP (cyclophosphamide, doxorubicin/hydroxydaunorubicin, vincristine/Oncovin, prednisone), together with the anthracycline-sparing variant CVP (cyclophosphamide, vincristine, prednisone) and the dose-intensified hyper-CVAD platform (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone)

used chiefly in acute lymphoblastic leukemia and Burkitt-type lymphoma, share the identical four-drug core of an alkylating agent, a vinca alkaloid, a corticosteroid, and a topoisomerase-active agent (etoposide in EPOCH; doxorubicin in CHOP and hyper-CVAD) [5,6,7]. Because these regimens are prescribed to overlapping patient populations, often as sequential or salvage options for the same individual, and because they share overlapping dose-limiting toxicities, a synthesis of the published toxicity literature across this regimen family is of direct clinical relevance to hematologists and medical oncologists managing treatment-related morbidity.

This case study assembles and narratively synthesizes retrospective cohort studies, phase II/III trial toxicity reports, pharmacovigilance analyses, and mechanistic reviews describing the toxicity profile of etoposide-prednisolone-vincristine-cycloph osphamide-containing regimens, organized thematically around the five toxicity domains most consistently reported in the literature: hematologic toxicity and myelosuppression, vincristine-induced peripheral neuropathy, cardiotoxicity, infection risk and febrile neutropenia, and cumulative-dose and comparative regimen-toxicity considerations, including cyclophosphamide-related genitourinary and corticosteroid-related metabolic effects. Rather than applying a systematic-review methodology with formal risk-of-bias scoring, this analysis follows the retrospective toxicity-profile format used elsewhere in this journal's Case Study series, drawing on individually verified, peer-reviewed sources to build a clinically oriented narrative of what is actually observed when these regimens are administered in practice.

Methods

This retrospective analysis was conducted as a targeted narrative synthesis rather than a formal systematic review. Candidate sources were identified through structured searches of PubMed, Journal of Clinical Oncology, Blood, the New England Journal of Medicine, and adjacent oncology and pharmacology journals, using search terms combining regimen names (EPOCH, DA-EPOCH-R, CHOP, R-CHOP, CVP, hyper-CVAD) with toxicity-domain terms (myelosuppression, febrile neutropenia, peripheral neuropathy, cardiotoxicity, hemorrhagic cystitis, cumulative dose). Sources were retained if they reported original retrospective cohort data, prospective trial toxicity outcomes, or narrative/mechanistic review content directly addressing the hematologic, neurologic, cardiac, infectious, or genitourinary and metabolic toxicity of a regimen built on the etoposide/doxorubici n-prednisolone-vincristine-cyclophosphamide core or a closely related backbone (CVP, hyper-CVAD). Each candidate reference was individually verified against its publisher or indexing record (title, author list, journal, year, volume, and digital object identifier or PubMed identifier) before inclusion; sources that could not be independently verified were excluded. Twenty-three sources met these criteria and form the basis of the synthesis presented below. Toxicity data extracted from each source were organized by domain rather than by regimen alone, consistent with a case-study format intended to describe the clinical pattern of toxicity encountered across this regimen family rather than to statistically pool effect estimates across heterogeneous study designs; where multiple studies reported quantitative incidence figures for a comparable toxicity within a comparable regimen and patient population, those figures are presented together in the tables and figure accompanying this analysis to illustrate the range and consistency of the reported estimates.

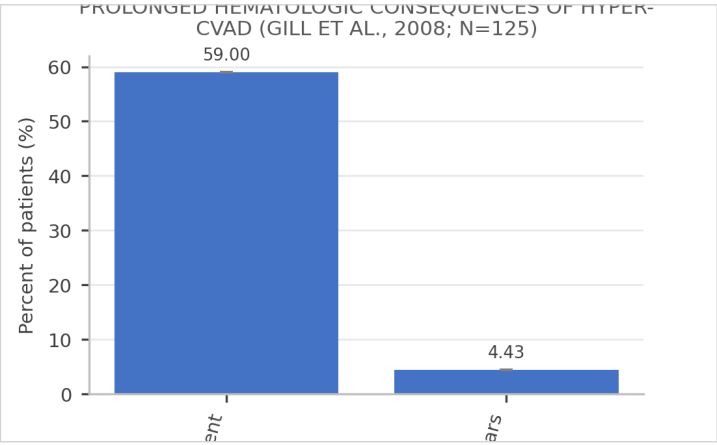
Hematologic Toxicity and Myelosuppression

Myelosuppression is the most universally reported dose-limiting toxicity across every regimen in this family, reflecting the combined marrow effects of the alkylating agent, the topoisomerase inhibitor or anthracycline, and, in dose-adjusted infusional schedules, deliberately escalated dosing driven by neutrophil nadir. In the original characterization of EPOCH in relapsed and refractory non-Hodgkin lymphoma, Wilson and colleagues reported that grade 4 neutropenia occurred in the substantial majority of treatment cycles, with the infusional schedule's dose-adjustment algorithm explicitly using the neutrophil nadir from the preceding cycle to titrate the subsequent cycle's dose upward or downward, a design feature that presupposes and manages severe but reversible myelosuppression as an expected on-target effect rather than an incidental toxicity [1]. The 8-year follow-up of this EPOCH experience confirmed that hematologic toxicity remained the dominant acute adverse effect through prolonged follow-up, with myelosuppression-related hospitalization and blood product support recurring across treatment courses without evidence of cumulative marrow exhaustion precluding further dosing in most patients [2]. When EPOCH was adapted to a first-line, rituximab-containing, dose-adjusted schedule for aggressive non-Hodgkin lymphoma, Lamar and colleagues similarly reported that grade 3-4 neutropenia was near-universal across treatment cycles, reinforcing that the dose-adjustment algorithm central to DA-EPOCH-R is fundamentally a hematologic-toxicity-driven titration system [8]. David and colleagues, reporting a dedicated complications analysis of DA-EPOCH-R in a real-world non-Hodgkin lymphoma cohort, similarly found hematologic toxicity, along with catheter-associated complications from the prolonged infusional administration schedule, to be the most frequent reasons for treatment modification or hospitalization [9].

The bolus-schedule CHOP backbone produces a qualitatively similar, though generally somewhat less severe, myelosuppressive pattern. Nickenig and colleagues' randomized comparison of CHOP against mitoxantrone-chlorambucil-prednisone (MCP) in follicular and mantle cell lymphoma found that CHOP produced lower hematologic toxicity than the comparator regimen despite achieving superior response rates, establishing that the specific combination of cyclophosphamide, doxorubicin, vincristine, and prednisone carries a comparatively favorable myelosuppression profile relative to at least one alternative alkylating-agent-based combination of similar clinical intent [5]. At the dose-intensified end of the spectrum, hyper-CVAD produces substantially more severe and, notably, more prolonged myelosuppression than either CHOP or standard-dose EPOCH. Kantarjian and colleagues' original report of hyper-CVAD in adult acute lymphocytic leukemia documented severe neutropenia and thrombocytopenia as expected, near-universal toxicities of the dose-intensive fractionated cyclophosphamide and high-dose cytarabine/methotrexate alternating cycles that constitute the full hyper-CVAD program [6]. Gill and colleagues extended this observation by specifically characterizing the duration of hematologic recovery after hyper-CVAD completion in a cohort of 125 consecutive patients, finding that cytopenias persisted in a majority of patients three months after treatment concluded, with full blood count normalization in most patients not occurring until six to nine months post-treatment, and a measurable cumulative incidence of secondary hematologic malignancy at four years of follow-up, an observation that is not typically

emphasized in shorter-term hyper-CVAD efficacy reports but that carries direct implications for post-treatment surveillance [10]. Taken together, these findings indicate that while all etoposide/doxorubicin-prednisolone-vincristine-cyclophosphamide-based regimens share myelosuppression as their dominant acute toxicity, the duration and depth of that myelosuppression scale directly with dose intensity and schedule complexity, from the comparatively self-limited CHOP pattern through the algorithmically managed but severe DA-EPOCH-R pattern to the prolonged, multi-month recovery trajectory documented after hyper-CVAD.

Prolonged and late hematologic consequences of the hyper-CVAD regimen in a cohort of 125 consecutive patients: the proportion with persistent cytopenia three months after treatment completion versus the cumulative incidence of a secondary hematologic malignancy at four years of follow-up, illustrating that dose-intensive regimens in this family carry hematologic risk well beyond the acute treatment period (Gill et al., 2008).



Vincristine-Induced Peripheral Neuropathy

Vincristine contributes a distinct, non-hematologic, cumulative and often dose-limiting toxicity to every regimen in this family: a predominantly sensory, length-dependent peripheral neuropathy arising from vincristine's disruption of axonal microtubule dynamics and consequent impairment of axonal transport. Triarico and colleagues' review of vincristine-induced peripheral neuropathy (VIPN) mechanisms in pediatric tumors summarizes the pathophysiological basis of this toxicity and catalogs the range of preventive and management strategies, including dose modification, that have been proposed, while emphasizing that no single intervention has yet been established as definitively neuroprotective without compromising vincristine's antitumor efficacy [11]. A substantial and rapidly growing pharmacogenomic literature has sought to explain the marked inter-patient variability in VIPN severity observed in clinical practice. Li and colleagues, studying two independent pediatric acute lymphoblastic leukemia cohorts, identified specific genetic variants, most prominently in the CEP72 gene, associated with increased susceptibility to VIPN, a finding independently reinforced by Yang and colleagues' review of genetic variation as a VIPN risk factor spanning CEP72, CYP3A5, and ABC-transporter family genes [12,13]. Mufti and colleagues extended this pharmacogenomic characterization with a genome-wide association analysis in a large pediatric cancer cohort, identifying an MCM3AP variant associated with a roughly six-fold increased risk of VIPN alongside a panel of twelve additional variants associated with apparent protection, collectively implicating genes governing nerve structure, myelination, neuronal transmission, and cytoskeletal function in determining individual VIPN susceptibility [14]. While this pharmacogenomic literature has been generated predominantly in pediatric acute lymphoblastic leukemia populations receiving vincristine outside the specific EPOCH/CHOP/CVP regimen context, the underlying pharmacological mechanism, and therefore the genetic risk architecture, is directly relevant to adult lymphoma patients receiving cumulative vincristine within these combination regimens, since the vincristine component and its dosing schedule are broadly comparable across pediatric leukemia and adult lymphoma protocols.

Clinically, peripheral neuropathy from vincristine-containing regimens such as CHOP and R-CHOP is reported to be common, cumulative across treatment cycles, and, in a meaningful proportion of patients, persistent well beyond treatment completion. Watson and colleagues' review of long-term consequences of the CHOP chemotherapy regimen situates peripheral neuropathy alongside cardiotoxicity as one of the two most clinically significant long-term, non-hematologic sequelae of CHOP-based treatment, noting that neuropathic symptoms can persist for months to years after the final vincristine dose and can meaningfully impair long-term quality of life even in patients who are otherwise cured of their lymphoma [15]. Because vincristine dosing is conventionally capped per administration (commonly at 2 mg per dose irrespective of body surface area) specifically to mitigate this toxicity, and because dose reduction or omission of vincristine is a recognized clinical strategy for managing emergent neuropathy during treatment, peripheral neuropathy functions as a practical, clinically visible dose-limiting toxicity for the vincristine component across the entire regimen family, in parallel with, but mechanistically independent from, the hematologic dose-limiting toxicity driven by the alkylating agent and topoisomerase-active or anthracycline components.

Cardiotoxicity

Cardiotoxicity in this regimen family arises predominantly from the anthracycline component (doxorubicin in CHOP and hyper-CVAD; doxorubicin is also incorporated into standard EPOCH, though not into the etoposide/prednisolone/vincristine/cyclophosphamide core in isolation), and to a lesser, less well-characterized degree from cyclophosphamide itself at conventional lymphoma-treatment doses. Rihackova and colleagues' review of treatment-related cardiotoxicity in malignant lymphoma catalogs anthracycline-mediated cardiomyopathy as the best-established cardiac toxicity in this treatment setting, driven mechanistically by topoisomerase-2-beta-mediated DNA damage and oxidative stress in cardiomyocytes, and note that both Hodgkin and non-Hodgkin lymphoma long-term survivors experience significantly elevated cardiovascular mortality relative to the general population, supporting long-term cardio-oncology surveillance as a standard component of post-treatment follow-up for patients who received an anthracycline-containing regimen from this family [16]. Septianda and colleagues' direct echocardiographic assessment of non-Hodgkin lymphoma patients treated with CHOP or CHOP-prednisolone regimens found measurable declines in left ventricular systolic function and detectable cardiac structural abnormalities attributable to the treatment regimen, providing direct clinical-imaging confirmation of the cardiotoxic potential of the CHOP backbone in a contemporary patient cohort rather than relying solely on historical or indirect evidence [17]. Lu and colleagues' systematic review and meta-analysis of cardiovascular adverse events

associated with the pegylated liposomal doxorubicin variant of this backbone, (R)-CDOP, used in patients considered to be at elevated risk of conventional anthracycline cardiotoxicity, found that even the liposomal reformulation carries a measurable, non-negligible cardiovascular adverse event rate, indicating that substituting the anthracycline delivery vehicle attenuates, but does not eliminate, this component of the regimen family's cardiotoxicity [18].

Cardiotoxicity within this regimen family is understood clinically to be substantially cumulative-dose dependent, with risk rising as a function of total anthracycline exposure across a patient's lifetime treatment history, a consideration of particular relevance for patients who receive an anthracycline-containing regimen from this family more than once, for example CHOP followed later by relapse treatment with a further anthracycline-containing salvage regimen, or EPOCH used as salvage after prior CHOP. Because cyclophosphamide is administered in every regimen surveyed in this analysis alongside the anthracycline (or, in EPOCH, alongside etoposide and doxorubicin together), and because cyclophosphamide has itself been associated with acute, high-dose-dependent cardiotoxicity most prominently at the substantially higher doses used in hematopoietic stem cell transplantation conditioning rather than at conventional lymphoma-treatment doses, the cardiotoxicity observed clinically at standard CHOP, EPOCH, or hyper-CVAD dosing in the lymphoma and leukemia literature synthesized here is attributed predominantly, though perhaps not exclusively, to the anthracycline component rather than to cyclophosphamide itself.

Infection Risk and Febrile Neutropenia

Febrile neutropenia is the clinically most consequential downstream complication of the hematologic toxicity described above and is separately and extensively documented in the literature on this regimen family, reflecting both its acute morbidity and its role as a key determinant of granulocyte colony-stimulating factor prophylaxis and dose-delay decision-making in routine practice. Choi and colleagues' analysis of neutropenia patterns and febrile neutropenia risk factors in diffuse large B-cell lymphoma patients treated with rituximab-CHOP found that a clinically significant proportion of patients experienced at least one febrile neutropenia episode over the course of treatment, with baseline patient characteristics including age and pre-treatment blood counts identified as significant predictors of subsequent febrile neutropenia risk, supporting individualized rather than uniform prophylactic strategies [19]. Matsuda and colleagues' nationwide Japanese real-world study focusing specifically on patients aged 80 years or older receiving their first R-CHOP cycle found a substantially elevated febrile neutropenia risk in this very elderly population relative to younger cohorts, directly implicating advanced age as a major, clinically actionable risk modifier for infectious complications of CHOP-based treatment and reinforcing current guideline recommendations for primary prophylactic growth factor support in older patients receiving anthracycline-containing regimens from this family [20].

The infusional, dose-adjusted EPOCH schedule introduces an additional infection-risk dimension distinct from CHOP-associated febrile neutropenia, related to the prolonged continuous intravenous infusion delivered via indwelling central venous catheter over multiple days per cycle. David and colleagues' complications analysis of DA-EPOCH-R identified catheter-related complications, including catheter-associated bloodstream infection, as a recurrent category of treatment-related morbidity specific to the infusional delivery method, occurring alongside, but mechanistically distinct from, neutropenia-related infection risk [9]. This distinction is clinically important: whereas febrile neutropenia risk in CHOP-based regimens is chiefly a function of marrow suppression depth and duration and is mitigated principally through growth factor support and dose adjustment, catheter-associated infection risk in EPOCH-based regimens additionally requires attention to line care, insertion-site surveillance, and the specific infection-control practices associated with ambulatory infusion pump management, representing a regimen-specific infection-risk consideration not shared by the bolus-schedule regimens in this family.

Cyclophosphamide-Related Genitourinary Toxicity and Corticosteroid Effects

Cyclophosphamide, present at broadly comparable per-cycle doses across EPOCH, CHOP, CVP, and hyper-CVAD, carries a well-characterized urothelial toxicity mediated by its acrolein metabolite, which is concentrated in and directly irritates the bladder urothelium, producing hemorrhagic cystitis in a dose-dependent manner. Almalag and colleagues' cohort study and literature review of hemorrhagic cystitis incidence after cyclophosphamide therapy, conducted specifically in the context of oncology treatment with and without the uroprotective agent mesna, found that hemorrhagic cystitis occurred in a measurable minority of patients receiving cyclophosphamide without mesna co-administration, with mesna use associated with meaningfully reduced incidence, supporting the now-standard practice of mesna co-administration alongside higher-dose cyclophosphamide regimens such as hyper-CVAD, while conventional CHOP- or EPOCH-level cyclophosphamide dosing is more commonly managed with hydration and monitoring alone rather than routine mesna prophylaxis [21]. Because hemorrhagic cystitis risk scales with cumulative and per-dose cyclophosphamide exposure, it is of particular relevance to hyper-CVAD, whose fractionated high-dose cyclophosphamide component substantially exceeds the cyclophosphamide dose delivered per cycle of standard CHOP or EPOCH, consistent with the more prominent role of mesna prophylaxis in hyper-CVAD treatment protocols relative to the other regimens in this family.

The corticosteroid component, prednisone or prednisolone, contributes a further, distinct set of toxicities that are frequently under-recognized relative to the hematologic, neurologic, and cardiac toxicities discussed above, despite being nearly universal in occurrence during active treatment. Watson and colleagues' review of long-term CHOP-regimen consequences specifically addresses corticosteroid-associated hyperglycemia, mood disturbance, and increased susceptibility to opportunistic infection as recurrent components of the overall CHOP toxicity burden, noting that these effects, while individually less severe than febrile neutropenia or cardiotoxicity, contribute cumulatively to the overall symptom burden and quality-of-life impact experienced by patients across a multi-cycle treatment course [15]. Corticosteroid-related and chemotherapy-related nausea and vomiting represent a further, highly prevalent, though largely preventable, component of the acute toxicity burden of this regimen family; Wakasugi and colleagues' retrospective comparison of antiemetic strategies in patients receiving CHOP or R-CHOP found that the addition of the neurokinin-1 receptor antagonist aprepitant to a serotonin-receptor-antagonist antiemetic backbone did not

significantly improve complete response rates for chemotherapy-induced nausea and vomiting relative to serotonin-receptor-antagonist monotherapy in this specific regimen context, an observation with direct implications for supportive-care resource allocation in routine CHOP and R-CHOP administration [22].

Comparative Regimen Toxicity and Cumulative Dose Effects

Direct or indirect comparison across the regimens surveyed in this analysis indicates a consistent gradient of overall toxicity burden that tracks dose intensity and schedule complexity rather than any single toxic component in isolation. CVP, lacking an anthracycline, carries the mildest overall toxicity profile among the regimens considered here, a feature explicitly exploited in Marcus and colleagues' randomized trial of rituximab plus CVP against CVP alone in advanced follicular lymphoma, in which CVP was selected as the chemotherapy backbone specifically because its comparatively favorable toxicity profile made it suitable for a typically older, often more comorbid follicular lymphoma population for whom anthracycline-containing regimens carry a less favorable risk-benefit balance [7]. Standard CHOP occupies an intermediate position, contributing the myelosuppression, cardiotoxicity, and vincristine-related neuropathy discussed throughout this analysis, but with a generally more favorable hematologic toxicity profile than at least some alternative anthracycline-free or alternative-alkylating-agent combinations, as demonstrated in the direct randomized comparison against MCP [5]. Standard-dose and dose-adjusted EPOCH, and its rituximab-containing derivative DA-EPOCH-R, present a toxicity profile broadly similar in kind to CHOP but generally more severe in hematologic terms, reflecting both the additional etoposide component and the explicit dose-adjustment algorithm that deliberately escalates dosing to the threshold of tolerable neutropenia [1,8,23]. Hyper-CVAD, at the most dose-intensive end of this spectrum, produces the most severe and most prolonged hematologic toxicity of any regimen surveyed, together with a comparatively elevated hemorrhagic cystitis risk necessitating routine mesna co-administration, findings that together explain why hyper-CVAD is generally reserved for younger, more treatment-fit patients with acute lymphoblastic leukemia or highly aggressive lymphoma rather than being used as a general-purpose lymphoma regimen [6,10].

Cumulative dose considerations are most clinically salient for the two components with well-established dose-toxicity relationships that persist or worsen with repeated exposure: the anthracycline component, whose cardiotoxicity risk accumulates across a patient's total lifetime anthracycline exposure and therefore constrains re-treatment options at relapse, and vincristine, whose neuropathy is similarly understood to accumulate across treatment cycles and to be influenced by inherited genetic susceptibility factors that are present, but not modifiable, at the time treatment is initiated [16,12,13,14]. Because these two cumulative toxicities are mechanistically independent of one another and of the hematologic and infectious toxicities discussed above, patients undergoing sequential or salvage treatment with more than one regimen from this family across the course of their disease accumulate risk along multiple independent toxicity axes simultaneously, a consideration that is not always explicitly addressed in individual regimen-specific toxicity reports but that emerges clearly when the literature on this regimen family is synthesized as a whole, as attempted in this analysis.

Conclusion

Principal toxicity domains reported for etoposide-prednisolone-vincristine-cyclophosphamide-based regimens and closely related backbones (CHOP, CVP, hyper-CVAD), with representative reference and clinical implication.

Regimen	Dominant toxicity domain(s)	Representative finding	Key reference
CVP	Mild myelosuppression; minimal cardiotoxicity (anthracycline-free)	Selected as backbone for older/comorbid follicular lymphoma patients due to favorable toxicity profile	Marcus et al. 2005
CHOP / R-CHOP	Myelosuppression, febrile neutropenia, vincristine neuropathy, anthracycline cardiotoxicity	Lower hematologic toxicity than MCP; LV systolic decline detectable by echocardiography; elevated febrile neutropenia risk in patients aged >=80	Nickenig et al. 2006; Septianda et al. 2025; Matsuda et al. 2022
EPOCH / DA-EPOCH-R	Severe, algorithmically-titrated myelosuppression; catheter-associated infection; neuropathy; cardiotoxicity	Near-universal grade 3-4 neutropenia driving dose-adjustment algorithm; catheter complications from infusional delivery	Wilson et al. 1993; Lamar et al. 2016; David et al. 2018
Hyper-CVAD	Severe, prolonged myelosuppression; hemorrhagic cystitis (high-dose cyclophosphamide)	Cytopenias persisting in most patients at 3 months; full recovery often delayed 6-9 months; secondary malignancy risk at 4 years	Kantarjian et al. 2000; Gill et al. 2008

The published retrospective, prospective trial, and mechanistic literature on etoposide-prednisolone-vincristine-cyclophosphami de-containing regimens and their close relatives (CHOP, CVP, and hyper-CVAD) describes a consistent, mechanistically coherent toxicity profile organized around five principal domains: myelosuppression, whose depth and duration scale with dose intensity from CVP through CHOP and EPOCH to hyper-CVAD; vincristine-induced peripheral neuropathy, a cumulative, genetically modulated toxicity shared identically across every regimen in this family; anthracycline-mediated cardiotoxicity, present in CHOP, EPOCH, and hyper-CVAD but absent from anthracycline-free CVP, and cumulative across a patient's total lifetime anthracycline exposure; febrile neutropenia and, in infusional EPOCH-based regimens, catheter-associated infection, whose risk is modified by age and baseline marrow reserve; and cyclophosphamide-related hemorrhagic cystitis together with corticosteroid-related metabolic and infectious effects, both of which scale with per-cycle alkylating-agent and corticosteroid dose. Clinicians selecting among this regimen family, or sequencing more than one of these regimens across a patient's treatment course, should weigh this shared and overlapping toxicity architecture explicitly, particularly with respect to cumulative anthracycline exposure and cumulative vincristine-associated neuropathy risk, rather than evaluating the toxicity of any single regimen in isolation. Continued pharmacovigilance and pharmacogenomic characterization, particularly of vincristine neuropathy risk and of long-term cardiovascular outcomes in lymphoma survivors, represents the

most promising direction for further reducing the treatment-related morbidity of this well-established and still widely used regimen family.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Ioannis Stavrou conceived the case study, conducted the literature search and verification, and drafted the manuscript. Ilze Krumins contributed hematologic and toxicology framing and critically revised the manuscript for important intellectual content. Toomas Oja contributed clinical pharmacology context and approved the final version for submission.

Ethics Statement

Not applicable. This is a retrospective narrative case-study analysis of previously published toxicity literature and did not involve new experimental data, identifiable individual patient records, human participants, or animal subjects.

Data Availability

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

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