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Exploring the burden of short-term CHOP chemotherapy adverse events in post-transplant lymphoproliferative disease: a comprehensive literature review in lymphoma patients

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ABSTRACT

Purpose: Cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) is a treatment for post-transplant lymphoproliferative disease (PTLD) following solid organ transplant (SOT) after failing rituximab, an aggressive and potentially fatal lymphoma. This study explores the humanistic and economic burden of CHOP-associated adverse events (AEs) in PTLD patients. Since PTLD is rare, searches included lymphoproliferative disease with lymphoma patients.

Design: This comprehensive literature review used the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) protocol, pre-specifying the search strategy and criteria. CHOP-associated short-term AEs with an incidence of >4% were sourced from published literature and cancer websites to inform the search strategy. PubMed and EMBASE searches were used to identify humanistic and economic burden studies.

Results: PubMed and EMBASE searches identified 3946 citations with 27 lymphoma studies included. Studies were methodologically heterogeneous. Febrile neutropenia (FN) was the AE most encountered, followed by chemotherapy-induced (CI) anemia (A), infection, CI-nausea and vomiting, thrombocytopenia, and CI-peripheral neuropathy (PN). FN and infections were associated with significant disutility, increased hospitalization, and extended length of stay (LOS). Infections and CIPN significantly impacted the utility of patients and CIA-related fatigue showed reductions in quality of life (QoL). Many patients continue to have QoL deficits continued even after AEs were treated. Management costs varied greatly, ranging from nominal (CIPN) to over $100,000 in the USA for infections, EUR 10,290 in Europe for infections, or CAN$1012 in Canada for FN. Cost of outpatient care varied but had a lower economic impact compared to hospitalizations.

Conclusions: Short-term AEs from CHOP in the lymphoma population were associated with substantial humanistic and economic burden.

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Stem cell transplant; lymphoproliferative disease; CHOP; adverse events; cost; resource use

Introduction

Post-transplant lymphoproliferative disease (PTLD) is a lymphoma that occurs following hematopoietic stem cell transplant (HCT) or solid organ transplant (SOT), which can be aggressive and often fatal if patients do not respond to treatment. Although no treatment is approved for PTLD, available initial treatment includes rituximab in both HCT and SOT patients[1–3]. Although some patients may initially respond to rituximab (with responses ranging up to 61%[4–12]) many patients will ultimately fail initial rituximab monotherapy and require additional treatment[4,5,7,13].

Although there is no standard of care in PTLD patients failing initial treatment[1–3], the cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy regimen with or without rituximab has been used to treat adult PTLD patients following SOT failing rituximab with some success with higher response rates in trials of sequential treatment[10,11]. CHOP salvage therapy in adult PTLD patients following HCT is generally not recommended as it has been associated with poor outcomes and a high mortality rate[3,6]. CHOP is also not generally used for the treatment of PTLD in children and adolescents, due to potential for short- and long-term adverse events (AEs) and treatment-related mortality (TRM)[14].

Unfortunately, the use of CHOP in PTLD following SOT in patients failing rituximab is also associated with significant TRM, with reported rates between 8 and 13%[10,11] and a substantial AE profile including 63–68% of patients with Grade 3 or 4 leukopenia and 34–41% of patients with Grade 3 or 4 infection[10,11]. These rates are high as complications from

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chemotherapy are far more common in SOT recipients than in the nontransplant population due to long-standing immunosuppression in these patients[15]. One study reported that 20% of patients had to switch to other less toxic monotherapies due to treatment-related AEs[16].

PTLD is rare[17], and its varied histological manifestations, combined with its medical complexity, have limited the availability of published studies in this therapeutic area. Studies available are characterized by substantial clinical and methodological heterogeneity[11,18].

Research directly addressing the burden of the CHOP regimen for PTLD is even more limited. The AE profile of the CHOP regimen is well-defined and it is likely that these AEs negatively affect quality of life (QoL) for SOT PTLD patients and increase health resource utilization and costs. This economic and humanistic burden arising from CHOP-emergent AEs in PTLD is yet to be characterized and the goal of this review was to identify available information.

Since PTLD is a rare disease[17], we anticipated that few (if any) eligible studies in this patient population would be identified. As PTLD is a type of lymphoma that can behave similarly to aggressive lymphomas, such as non-Hodgkin lymphoma (NHL), this search considered all lymphoproliferative disease patients with lymphoma to maximize the opportunity to identify useful information regarding economic and humanistic burden.

Objective

To perform a comprehensive literature review to understand the humanistic and economic consequences associated with CHOP-emergent short-term AEs in patients with PTLD and lymphoproliferative disease with lymphoma.

Materials and methods

This comprehensive literature review used the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) protocol wherein the research question (using the population, intervention, comparator, outcomes, study [PICOS] format), search strategy, target short-term AEs, and inclusion and exclusion criteria were pre-specified in detail (Table 1).

Studies were eligible for inclusion provided that the patient population were PTLD or lymphoproliferative disease with lymphoma patients treated with the CHOP regimen or one or more of its individual components. Studies incorporating rituximab alongside CHOP (CHOP + R) were also included as the strategy represents a valid treatment option for PTLD patients. Relevant short-term AEs associated with CHOP were sourced from the published literature[19,20] and validated by patient regimen guides from cancer.gov[21] and Cancer Research UK[22]. There was a focus on events that were of greater severity (of Grade 3 or 4) with an incidence greater than 4%.

Population and AE terms were combined with terms relating to humanistic and economic burden as part of two search strategies: one using specific descriptors for each AE of interest (i.e. leukopenia, anemia [A], etc.) and second, general search identifying the impact of AEs in aggregate (i.e. using terms, such as "adverse event" or "adverse effect") (Table S1). Population terms were kept broad, focusing on all lymphoproliferative diseases, in order to avoid missing

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
(P) Population- and disease-related criteria	
Adults and children (no age restrictions) with PTLD or lymphoproliferative disease with lymphoma and experiencing a short-term adverse event of interest: Neutropenia and febrile neutropenia, Leukopenia, Lymphopenia, Thrombocytopenia, Dyspnea, Anemia, Pneumonia and other infections, Sepsis, Acute renal failure, Acute hepatitis, Nausea and vomiting, Cystitis, Diarrhea, Peripheral neuropathy, Edema, Pain	Publications not focused on PTLD or lymphoma or on AEs not considered "short-term" (treatment-emergent within one month of treatment cessation) or on other AEs
(IC) Intervention- and comparator-related criteria	
The CHOP protocol and its individual components (vincristine, cyclophosphamide, prednisone, doxorubicin).	Other regimens
(O) Outcome-related criteria	
Healthcare costs and resource use Utilities, disutilities, and other QoL-related information	Other outcomes
(S) Study design-related criteria	
Including, but not limited to: Randomized controlled trials, Observational study, Cross-sectional study, Systematic review, Case series ($n > 20$)	Other study types (News, Video-audio media, Webcast, Case reports, Case series ($n < 20$), Letter, Commentary, Review, Treatment/practice guidelines, Consensus development, Notes)
Publication year	
Published after a January 2000 [for utility literature] Published after 1 January 2012 [for cost and resource utilization literature]	Published before 1 January 2000 [for utility literature] Published before 1 January 2012 [for cost and resource utilization literature]
Study country (i.e.s)	
United States, Canada, EU	Other countries
Publication language	
English. Information from foreign language publications with English abstracts will be included.	Languages other than English
Document type/study design-related	
Randomized controlled trials, Observational study, Cross-sectional study, Systematic review, Case series ($n > 20$)	Other study types (News, Video-audio media, Webcast, Case reports, Case series ($n < 20$), Letter, Commentary, Review, Treatment/practice guidelines, Consensus development, Notes)

Inclusion and exclusion criteria that governed the conduct of the review. AEs, Adverse events; QoL, Quality of life; EU, European Union; PTLD, Post-transplant lymphoproliferative disorder.

relevant studies. Economic burden was defined as the management costs and resource utilization associated with treating CHOP-emergent AEs, and the humanistic burden was defined as the utility, disutility, or HRQoL impact of CHOP-emergent AEs. Studies without an English language abstract or originating from outside United States of America (USA), Canada, and Europe (European Union [EU]) were not eligible for abstraction. Searches were restricted from year 2000 onwards for humanistic burden studies and from 2010 onwards for economic burden studies. Both searches were executed in PubMed and EMBASE during December 2018.

Screening was undertaken using pre-specified criteria by two reviewers. Study selection was guided by PICOS and inclusion/exclusion criteria (Table 1), with reasons for exclusion noted and all identified papers accounted for. Reference lists of included systematic reviews were screened for additional studies not already identified. A data extraction form was developed to systematically capture data pertaining to healthcare resource utilization (HRU), costs, and humanistic burden from each article meeting the inclusion criteria. While data was extracted across all pre-specified AEs, results were summarized only for those AEs for which three or more papers were included.

Results

Study characteristics

In total 3946 citations were retrieved and screened across both search strategies and databases, of which 27 ultimately met the search criteria (Figure 1). Lymphoproliferative disease studies recruiting lymphoma patients most commonly included non-Hodgkin's lymphoma (NHL), diffuse large B-cell lymphoma, and follicular lymphoma. Febrile neutropenia (FN) was the AE most commonly encountered (Figure 2(A)), followed by chemotherapy-induced anemia (CIA), infection, chemotherapy-induced nausea and vomiting (CINV), thrombocytopenia, and chemotherapy-induced peripheral neuropathy (CIPN). Most studies reported data for the R-CHOP or CHOP treatment regimen; 30% reported a mix of chemotherapies (Figure 2(B)). Methodological approach employed varied with around 40% based on some form of retrospective analysis or prospective observational study (Figure 2(C)). Cost-effectiveness models and randomized controlled trials (RCTs) were also frequently retrieved (37 and 11%, respectively). Studies recruiting an EU population accounted for the greatest proportion of research (41%) (Figure 2(D)).

Summary findings: febrile neutropenia (16 studies[23–38])

Sixteen studies addressed FN following chemotherapy. A patient's first FN episode was most likely to occur during the first cycle of chemotherapy[24,26,34]. In both the US and EU/Canada, FN events were predominantly treated in the inpatient setting[30,38]. In the USA, up to 84% of patients require at least one hospitalization[29] and many require multiple hospitalizations[24]. Mean hospital length of stay (LOS) for patients with FN varied (range: 7.9–9.8 d in the USA[24,31,36] and 6–11.8 in EU/Canada[26,28,30,34,38]) Mean LOS

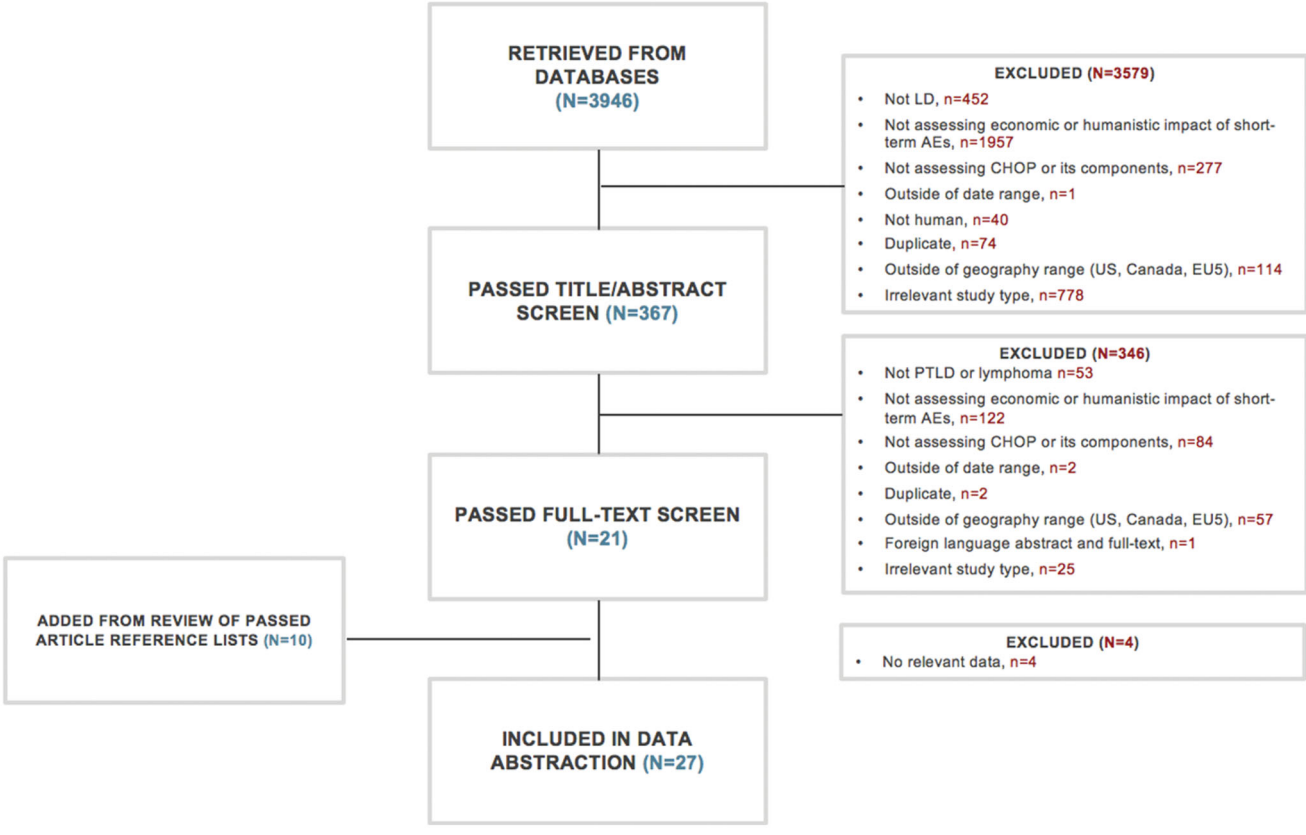

Figure 1. Flow-chart accounting for study inclusion and exclusion. AE, Adverse event; CHOP, Cyclophosphamide, doxorubicin, vincristine, prednisone; EU5, 5 European countries (France, Germany, United Kingdom, Spain, Italy); LD, Lymphoproliferative disease; PTLD, Post-transplant lymphoproliferative disease; US, United States.

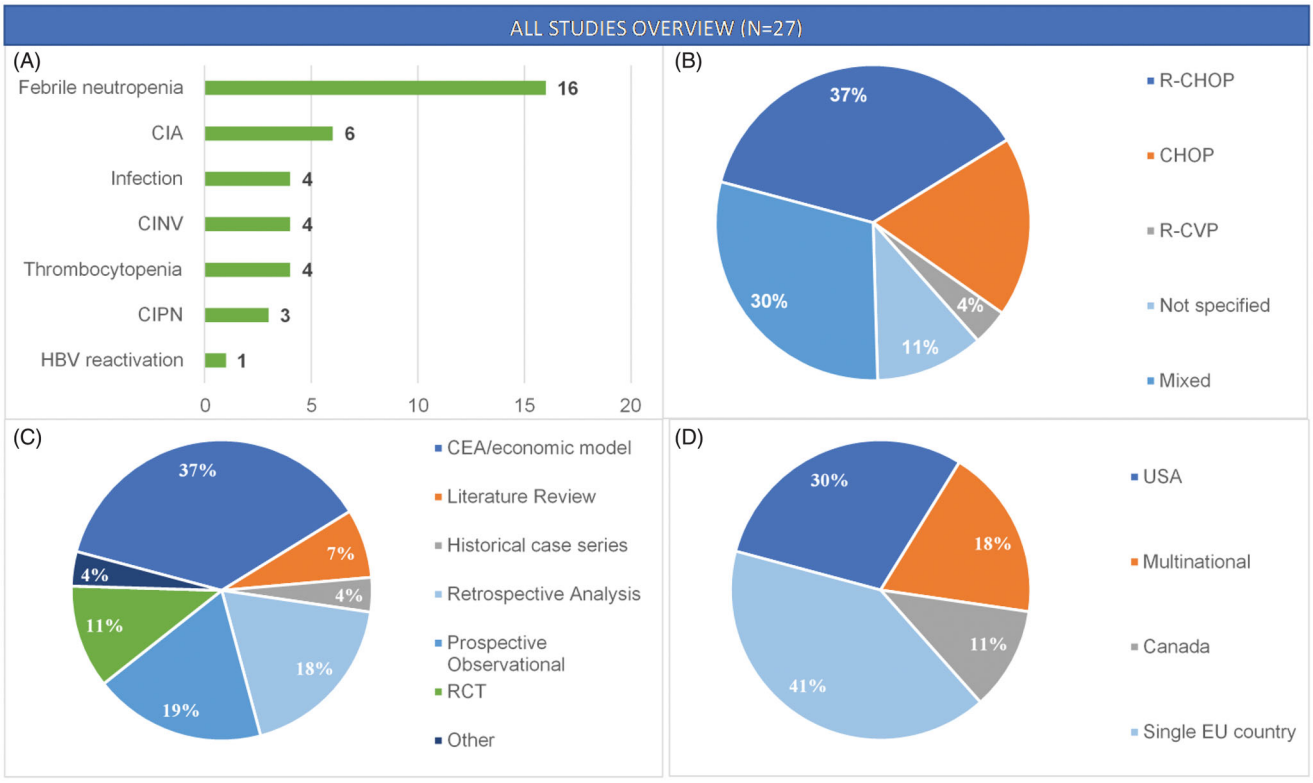

Figure 2. Overview of adverse event, chemotherapy, study type, and country of origin for included studies. Panel A: Sum of studies of studies here exceeds 27 as several contributed data to more than one adverse event category. CIA, Chemotherapy-induced anemia; CINV, Chemotherapy-induced nausea and vomiting; CIPN, Chemotherapy-induced peripheral neuropathy; HBV, Hepatitis B Virus. Panel B: Type of chemotherapy reported by each included paper. CHOP, Vincristine, cyclophosphamide, prednisone, doxorubicin; CVP, Cyclophosphamide, vincristine, prednisone; R, Rituximab. Panel C: Study type recorded for each included study; CEA, Cost- effectiveness analysis; RCT, Randomized controlled trial. Panel D: Country of origin; USA, United States of America; EU, European Union.

Table 2. Impact of FN on mean or median hospital length of stay.

References	Study type (*N*)	Population	Endpoint	Regimen	Value
Chrischilles et al.[24]	Historical case series (577)	NHL	Mean LOS	CHOP	8.3 d (patients with 1 hospitalization)
Fust et al.[28]	CEA (N/A)	NHL	Mean LOS	R-CHOP	10.7 d
Issa et al.[30]	Retrospective analysis (273)	NHL	Median LOS	CHOP/R CHOP/CVP/CVP + and other single agents	11.8 d
Kawatkar et al.[31]	Retrospective analysis (581)	NHL	Mean LOS	CHOP ± R	7.9 d
Pettengell et al.[34]	Retrospective analysis (1111)	DLBCL	Mean LOS	R-CHOP	9.6–12.9 d
Weycker et al. [38]	Retrospective analysis (590)	NHL	Mean LOS	CHOP ± R	6.2 d
Doorduijn et al.[26]	RCT (389)	NHL	Median LOS	CHOP	6.0 d
Wang et al.[36]	Retrospective analysis (4313)	NHL	Mean LOS	Mixed (R-CHOP, R-CVP, R, R-CD)	9.8 d

CEA, Cost-effectiveness analysis; d, Day; DLBCL, Diffuse large B-cell lymphoma; FN, Febrile neutropenia; ICU, Intensive care unit; LOS, Length of stay; NHL, Non-Hodgkin's lymphoma; RCT, Randomized controlled trial; N/A, Not available; CHOP, Cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CD, rituximab, cyclophosphamide, dexamethasone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R, rituximab.

was longer in FN patients with multiple hospitalizations[24], older patients[24], and patients with comorbidities[30] (Table 2). Patients with FN also required additional office visits and other procedures[30,31,38].

In both the US and EU, inpatient costs attributable to FN were $33,006 per episode in the most recent US study[31] and CAN$1012/d in the most recent EU/Canada study[32], and were the primary driver of total costs (Table 3). Inpatient costs were higher during the first treatment cycle[38]. Outpatient costs were variable but generally less than inpatient costs (Table 3). Some patients with FN also require additional procedures and office visits[30,31,38]. In addition, a systematic literature review found that indirect costs represent as much as 11% of all FN-associated costs[37].

Although granulocyte colony-stimulating factor treatment (G-CSFs) may be used for the prevention and/or treatment of FN, prophylaxis (primary and secondary) was more common[31,39] and continued for up to 5 d[36]. Mean LOS was increased by 5.13 d in those not receiving G-CSFs[24]. Up to 54% of patients with FN also receive treatment with antibiotics.

Utility measures of QoL, ranges between 0 (equal to death) and 1 (equal to perfect health), and reflects preference values that patients attach to their health state. The

Table 3. Costs (outpatient, inpatient, and total) associated with FN in chemotherapy-treated lymphoma patients.

References	Study type (*N*)	Population	Regimen	Endpoint	Value	Cost type
Outpatient						
Wang et al.[36]	Retrospective analysis (4313)	NHL	Mixed (R-CHOP, R-CVP, R, R-CD)	Mean FN-related total outpatient costs	$1046	2010 USD. Paid claims.
Hill et al.[29]	CEA (N/A)	NHL	CHOP ± R	FN outpatient cost FN post-hospitalization costs	$7667 $3932	2012 USD. Cost type not specified.
Kawatkar et al.[31]	Retrospective analysis (581)	NHL	CHOP ± R	Overall average ED costs in patients with FN Overall average office visit costs for patients with FN	$1729 $2813	2013 USD. Based on 2012 MEPS Survey
Weycker et al.[38]	Retrospective analysis (590)	NHL	CHOP ± R	Mean overall FN-related costs attributable to outpatient care/ home care	GBP 180/GBP 1673	2010 GBP (NHS reference costs)
Fust et al.[28]	CEA (N/A)	NHL	R-CHOP	FN outpatient cost FN post-hospitalization cost	EUR 1034 (16% of inpatient cost) EUR 2069 (32% of inpatient)	2014 EUR. Cost type not specified.
Inpatient						
Chan et al.[23]	CEA (N/A)	DLBCL	R-CHOP	Cost of FN hospitalization (9 days assumed)	C$13,467	Case costing data from hospitals
Lathia et al.[32]	CEA (N/A)	DLBCL	R-CHOP	FN hospitalization cost per day	C$1012	2012 CAD. Costs from "provider perspective".
Fust et al.[28]	CEA (N/A)	NHL	R-CHOP	FN hospitalization cost per event	EUR 7138	2014 EUR. Cost type not specified.
Weycker et al. [38]	Retrospective analysis (590)	NHL	CHOP ± R	Mean overall FN-related costs attributable to inpatient care	GBP 6007	2010 GBP (NHS reference costs)
Kawatkar et al.[31]	Retrospective analysis (581)	NHL	CHOP ± R	Overall average inpatient costs in patients with FN	$33,006	2013 USD. Based on 2012 MEPS Survey and per diem inpatient costs.
Total						
Weycker et al.[38]	Retrospective analysis (590)	NHL	CHOP ± R	Mean overall FN-related costs	GBP 8066	2010 GBP (NHS reference costs)
Kawatkar et al.[31]	Retrospective analysis (581)	NHL	CHOP ± R	Overall average total costs in patients with FN	$37,555	2013 USD. Based on 2012 MEPS Survey and per diem inpatient costs.
Wang et al.[36]	Retrospective analysis (4313)	NHL	Mixed (R-CHOP, R-CVP, R, R-CD)	Mean FN-related total medical costs	$41,483	2010 USD. Paid claims.
Sabater et al.[35]	CEA (N/A)	Follicular lymphoma	R-CHOP	Management cost per neutropenic/FN event	EUR 282/EUR 2036	EUR 2013. Cost type not reported (based on expert opinion).
Papaioannou et al.[33]	CEA (N/A)	Follicular lymphoma	R-CHOP, R-CVP	Management cost per neutropenic event	GBP 3272	Cost type and year not reported. Taken from manufacturer submission.
Dewilde et al.[25]	CEA (N/A)	Follicular lymphoma	R-CHOP	Management cost per neutropenic/FN event	GBP 3362/GBP 5373	GBP 2011. NHS reference costs.

CEA, Cost-effectiveness analysis; DLBCL, Diffuse large B-cell lymphoma; FN, Febrile neutropenia; ICU, Intensive care unit; LOS, Length of stay; NHL, Non-Hodgkin's lymphoma; RCT, Randomized controlled trial; EUR, Euro; CAD, Canadian Dollar; USD, United States Dollar; NA, Not applicable; ED, Emergency Department; R-CD, Rituximab, cyclophosphamide, dexamethasone; R-CVP, Rituximab, cyclophosphamide, vincristine, prednisolone; R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; MEPS, Medical Expenditure Panel Survey; NHS, National Health Service; GBP, Great British Pound; ED, Emergency Department; R, Rituximab

utility values used in cost-effectiveness models for NHL patients hospitalized with FN ranges from 0.33 to 0.36[23,28,29], such low scores have been associated with disease relapse in leukemia patients[40]. A disutility (or a reduction in utility) of 0.15 for patients hospitalized with FN has also been cited[32].

Summary findings: chemotherapy-induced anemia (CIA) (6 studies[25,33,35,41–43])

Six studies reporting information relating to CIA in lymphoma were included. Other than potential hospitalization, erythropoeitin stimulating agents (ESA) use and red blood cell (RBC) transfusions represent two of the main cost and resource drivers. RBC transfusion rates up to 58% were reported[41–43]. Although transfusion rates were attenuated by ESA use, a significant proportion of CIA NHL patients receiving ESAs still required transfusions[43].

CIA management costs associated with CHOP or some variation have been included in several economic modeling studies but they focus on inpatient costs only, and are largely not contemporary estimates (pre-2014)[25,33,35]. One Dutch study reported other medical resource use associated

with CIA limited to moderate costs associated with transfusion (costs of RBCs transfused EUR 398 to EUR 553 (cost year not stated)[42])

The Functional Assessment of Cancer Therapy – Anemia (FACT-An) is a measure of the impact of A associated with cancer therapies on patient QoL. The FACT-An (and subscales addressing physical well-being, social/family well-being, emotional well-being, and functional well-being) and visual analog scales (a visual line labeled with a 1–10 or 1–100 scale) documented significant functional impairment associated with CIA[43].

Summary findings: infection (four studies[33,35,41,44])

Four relevant CHOP-associated infection studies were identified. Clostridium difficile infection (CDI) and sepsis, as well as infection generally, were associated with long hospital lengths of stay compared to patients without infection. Mean LOS for patients with CDI was 23.6 d (*versus* 9.9 d without CDI) and mean LOS per sepsis complication was 8 d[41,44].

Infectious comorbidities were costly, with the charges made by US hospitals of $197,015 with CDI and $79,392 without CDI (USD hospital charges[44]) Costs were attributed to prolonged hospitalization with complicated and costly procedures. Costs of management per sepsis/infection event in the EU were EUR 10,290 (2013 EUR)[35] and GBP 1077 (cost year not stated[33]).

Summary findings: chemotherapy-induced nausea and vomiting (CINV) (four studies[26,45–47])

Although four studies reporting CINV data were included, no studies were identified assessing the economic impact of CINV in lymphoma patients. The impact of CINV appeared to be transient with HRQoL returning to levels similar to the general reference population. The EORTC QLQ-C30 nausea/vomiting subscale score (a specific scale within the EORTC QLQ-C30 addressing the impact of nausea/vomiting on patient HRQoL) indicated that this event was the least burdensome of all symptoms assessed by this measure (fatigue, pain, and nausea/vomiting); although scores do increase (worsen) during treatment, the overall humanistic impact remained low[45–47]. Data from other measures corroborated the low humanistic burden associated with CINV, especially when compared to other AEs of interest[26].

Summary findings: thrombocytopenia (4 studies[25,35,41,42])

Four studies provided data for the treatment of thrombocytopenia in relation to CHOP chemotherapy in lymphoma. Platelet transfusions for Grade 3 or 4 thrombocytopenia were infrequently reported[25,35] and overall transfusion rates varied between 2 and 6%[41,42]. Thrombocytopenia was typically one of the least costly AEs to treat as characterized by the unit and platelet transfusion costs reported[25,35,42].

Summary findings: pain and chemotherapy-induced peripheral neuropathy (CIPN) (three studies[35,46,47])

CIPN is typically associated with vinca alkaloids such as vincristine[48] and available cost data were from only one economic modeling study set in Spain and suggested that CIPN was typically one of the least costly AEs to treat. This study reported that Grade 3/4 CIPN affected only 3% of R-CHOP patients at a unit cost of EUR 92.09 (2013 EUR)[35]. Three further studies suggest that patients without a diagnosis of CIPN typically report insignificant symptoms on pain symptom scales with minimal short-term and/or long-term HRQoL impact[46,47]. No other data was available.

Discussion

This is the first study to examine the economic and humanistic burden of CHOP-related short-term AEs in lymphoproliferative disease patients with lymphoma. This study aimed to evaluate the economic and humanistic burden of short-term AEs due to CHOP in PTLD patients; however, due to the rarity and limited data of PTLD and that PTLD is a type of lymphoma that can behave similarly to aggressive lymphomas, this study was expanded to include lymphoproliferative disease patients with any kind of lymphoma as a suitable proxy population.

Although lymphoma provided a clinically relevant proxy patient population for PTLD, it may lead to an underestimate of the economic and humanistic burden of PTLD. The complications from chemotherapy, such as infections, are far more common in transplant recipients than in the nontransplant population due to long-standing immunosuppression (63% to 68% of PTLD patients treated with CHOP following rituximab failure developed Grade 3 or 4 leukopenia and 34% to 41% Grade 3 or 4 infection[10,11,15,16]) Chemotherapy-related mortality is also exacerbated in PTLD patients relative to lymphoma patients: PTLD is associated with 8% to 13% chemotherapy-related mortality, which is at least two to three times higher than in non-transplant diffuse large B-cell lymphoma[10,11,13,16,20,49,50]. Therefore, the incidence of short-term AEs associated with CHOP (FN, infection, CIA, CIPN, CINV, and thrombocytopenia), and the economic and humanistic burden they present, is likely to be much greater in PTLD patients than in the lymphoma population observed in the included studies.

HRU burden

Hospitalization was the most often studied element of HRU, owing largely to its potential as a cost driver; studies suggested that toxicity management was an important reason for inpatient admission and rehospitalization. Hospital LOS was substantial particularly for FN and infections and ranged from 6 to 24 d. Although hospitalization was likely the most important component of medical resource use, the burden of ongoing clinician visits, diagnostic tests, and long-term or chronic treatment should not be underestimated. Several studies attempted to evaluate the degree to which medical

resource use (e.g. ESAs, G-CSF, and antibiotics) may offset the need for expensive (i.e. hospitalization) or constrained (i.e. RBCs, transfusions) resources; the magnitude of such benefit varied.

Economic burden

The costs of managing AEs related to CHOP components were highly variable, ranging from nominal cost for events such as peripheral neuropathy (PN) to as high as USD 197,000 for infections in the US, EUR 10,290 for infections in the EU, or CAN$1012 for FN in Canada. Costs were notably higher in the US than EU. The majority of AE-related costs were incurred early, usually during the first chemotherapy cycle; although some events occurred with increasing chemotherapy exposure, they tended to be less costly to manage. Costs associated with chemotherapy-related toxicities tend to be nearly exclusively medical-related; few studies evaluating indirect costs (e.g. lost productivity) appeared in our review. Hospitalization was a key driver for increased costs; the cost of outpatient care and therapeutic products (e.g. ESAs, transfusions, and pharmaceuticals) varied by type of AE but were not key cost drivers. Some AEs, in particular FN, can be partially managed through primary or secondary prophylaxis with agents such as filgrastim and pegfilgrastim. As biosimilars for these products are now available, the overall economic burden from FN may now be lower than the values reported in this review.

Humanistic burden

The humanistic burden of AEs was not addressed in detail by many identified studies. Health preference for CHOP-related AEs was infrequently reported. The disutility for CHOP-related FN was significant (−0.15) and aligned with the impact of functional limitations on HRQoL in older adults[51]. CIA-related fatigue, as measured by FACT-An, indicated substantial functional impairment and reduced patient QoL. EORTC-QLQ-C30 was commonly used to document HRQoL impairment associated with toxicity-related AEs such as CIPN and CINV, with most detrimental CHOP effects normalizing over an extended period. The evidence for a positive HRQoL benefit associated with some AE treatments (e.g. ESAs, G-CSF) suggests many patients likely remain with HRQoL deficits even after treatment.

Study limitations

This comprehensive literature review took a pragmatic approach and was not intended to be systematic in nature. It is important to acknowledge that efforts were taken to ensure that relevant literature was identified and bias minimized. Similar to a systematic literature review, two databases were searched, screening was undertaken using pre-specified criteria by two reviewers, reasons for exclusion were noted, and all identified papers accounted for. The main difference is that quality appraisal was not undertaken, since humanistic and economic literature are mainly real-world studies with less emphasis on RCTs. The heterogeneity in methodological approach, target populations, treatments, study time frames, and perspectives prevented an informative comparison between most studies and results were presented as a qualitative summation only.

Short-term adverse effects are only part of the clinical picture of chemotherapy use. Historically, TRM rates for chemotherapy in PTLD patients were high[3,52,53] but more refined treatment approaches have improved survival, although chemotherapy TRM is still significant with rates between 8 and 13%[10,16,54]. For patients surviving chemotherapy, potential late-onset adverse effects (that persist or arise two or more years after CHOP chemotherapy treatment) are also likely a key driver of economic and humanistic burden. Evidence from the use of CHOP or its components in treatment of children with acute myeloid leukemia or other childhood cancers suggests that testicular and ovarian dysfunction (which may lead to delayed or arrested puberty, premature menopause, impaired fertility, and infertility), urinary tract toxicity and bladder malignancy, acute myeloid leukemia, cardiac complications (cardiomyopathy, arrhythmia, and subclinical left ventricular dysfunction), peripheral sensory or motor neuropathy, reduced bone mineral density, neurocognitive deficits, and cataracts remain of particular concern[49]. These health issues may arise years after treatment cessation and were not sought in this review.

Conclusions

In this comprehensive literature review, we did not identify any economic or humanistic data attributable to chemotherapy-related AEs in the PTLD population, most likely due to the rarity of the disease. By undertaking a comprehensive review in a proxy population, we have developed an approach to exploring burden of disease in a rare population where no data on the topic yet exists. In summary, while chemotherapy may be a commonly used standard of care in PTLD patients, particularly those post-SOT, the short-term adverse effects of the CHOP chemotherapy regimens are associated with a substantial economic and humanistic burden in the PTLD-like population of lymphoma patients. Given that PTLD patients are significantly more immunocompromised than patients with lymphoma, the already significant burden of chemotherapy-related AEs is likely to only be exacerbated in this population. This review crystallizes the need for effective therapies for patients with PTLD that are not associated with the burdensome short-term side effects, and associated humanistic and economic costs, of chemotherapy.

Transparency

Declaration of funding

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Declaration of financial/other relationships

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Previous presentations

None.

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