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ORIGINAL ARTICLE

A review of the risks of long-term consequences associated with components of the CHOP chemotherapy regimen

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ABSTRACT

A common chemotherapy regimen in post-transplant lymphoproliferative disease (PTLD) following solid organ transplants (SOT) is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). This study reviews the quantitative evidence for long-term consequences associated with components of CHOP identified from the Children's Oncology Group Long-Term Follow-Up Guidelines. Cited references were screened using prespecified criteria (English, systematic review, randomized controlled trial $n > 100$, observation study $n > 100$, case series $n > 20$). Relevant data were extracted and synthesized. Of 61 studies, 66% were retrospective cohort studies, 28% were in the US, and 95% enrolled pediatric patients. No study focused specifically on the CHOP regimen. Long-term consequences for CHOP components observed in >3 studies included cardiac toxicity ($n = 14$), hormone deficiencies/infertility ($n = 14$), secondary leukemia ($n = 7$), osteonecrosis ($n = 6$), and bladder cancer ($n = 4$). These effects are significant, impact a high percentage of patients, and occur as early as one year after treatment. Although none of the studies focused specifically on the CHOP regimen, 30%, 23%, and 15% evaluated alkylating agents (e.g. cyclophosphamide), anthracyclines (e.g. doxorubicin), and corticosteroids (e.g. prednisone), respectively. All three product classes had a dose-dependent risk of long-term consequences with up to 13.2-fold, 27-fold, 16-fold, 14.5-fold, and 6.2-fold increase in risk of heart failure, early menopause, secondary leukemia, bladder cancer, and osteonecrosis, respectively. Lymphoma patients had significantly elevated risks of cardiac toxicity (up to 12.2-fold), ovarian failure (up to 3.8-fold), and osteonecrosis (up to 6.7-fold). No studies were found in PTLD or SOT. Safe and effective PTLD treatments that potentially avoid these long-term consequences are urgently needed.

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CHOP; adverse events; long-term outcomes; stem cell transplant; lymphoproliferative disease

Introduction

Post-transplant lymphoproliferative disease (PTLD) is a lymphoma following solid organ transplant (SOT) or hematopoietic stem cell transplant (HCT) that can be aggressive and often rapidly fatal for patients who do not respond to treatment. PTLD currently has no approved treatment options. Initial treatment often includes rituximab[1–3], and although many SOT and HCT patients may respond initially (response rates up to 61% are reported[4–12]), some patients will ultimately fail and require additional treatment[4,5,7,13].

There is no defined standard of care for those PTLD patients who require further treatment[1–3]; however, the cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy regimen (with or without rituximab) has been used. Adult SOT PTLD patients initiating with rituximab and CHOP in combination or failing rituximab and subsequently treated with CHOP have experienced some success, particularly in trials of sequential treatment[10,11], but salvage treatment with CHOP in HCT PTLD patients has been associated with poor outcomes and high mortality[3,6].

The use of CHOP in PTLD and other lymphomas is associated with a significant short-term adverse event burden characterized by febrile neutropenia, anemia, infection, nausea, vomiting, thrombocytopenia, and peripheral neuropathy[14]. For surviving patients, there is also an increased focus on longer term adverse effects that may arise in the years following treatment. The long-term consequences of CHOP in terms of the incidence, timing, and risk factors associated with these events remain poorly understood, particularly for PTLD and immunocompromised transplant patients. This research aims to identify, summarize, and most importantly, to quantify long-term adverse consequences of components of CHOP treatment.

As PTLD is a rare disease, we anticipated that few (if any) relevant studies would be identified addressing the long-term adverse consequences of CHOP or CHOP components specifically in the PTLD patient population. This anticipated absence of evidence for PTLD means that a broader perspective (including the consequences of CHOP for other cancers where CHOP or CHOP components are an established treatment with an established safety profile) is more likely to identify relevant information. Notably, we also sought

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research that addressed the long-term consequences of CHOP or CHOP components in survivors of cancers diagnosed during childhood, adolescence, or young adulthood. Firstly, because long-term or delayed adverse effects are more likely observed for a longer period of follow-up in a younger patient group and can be matched more readily to a sibling as a control. Secondly, because the pediatric population is also particularly relevant to PTLD as children and young adults are most vulnerable and younger patients tend to be those most impacted by PTLD[15].

To achieve this broader perspective and quantify the long-term consequences in a pediatric cancer survivor population previously treated with CHOP or a CHOP component, this review built upon the evidence already identified by the Children's Oncology Group Long-Term Follow-Up Guidelines (COG LTFU) guidelines[16]. The COG LTFU guidelines were developed to increase awareness and provide recommendations for the screening and management of long-term consequences in survivors of pediatric malignancies based on risk and exposure of therapies, including chemotherapies. These recommendations are based upon an ongoing extensive review of available medical literature (most recently updated in 2018) and although the results subject to rigorous analysis and comprehensive review by a panel of 62 experts in the late effects of pediatric malignancies, the guidelines do not quantify the long-term treatment consequences across included studies.

This study describes and quantifies the long-term treatment-related consequences (defined as therapy-related complications that persist or arise after treatment) associated with the CHOP regimen in pediatric cancer survivors, drawing upon evidence collected in the COG LTFU guidelines. We sought to systematically synthesize relevant data to quantify the risk of these consequences in terms of magnitude (how many patients are likely to be impacted), timing (time to onset of the effects), and relationship to other factors such as dosage and patient characteristics.

Methods

Potential long-term consequences of CHOP components and their class of treatments were identified from the COG LTFU guidelines. Citations from the COG LTFU guidelines for these long-term consequences were screened against the inclusion and exclusion criteria prespecified in the protocol (Table 1).

Systematic reviews, randomized controlled trials ($n > 100$), observation studies (>100), cross-sectional studies ($n > 100$), or case series ($n > 20$) were sought reporting therapy-related consequences for cancer survivors originally treated with the CHOP protocol and/or its constituent components (cyclophosphamide, doxorubicin, vincristine, prednisone). Outcomes of interest included the incidence, prevalence, time to development of complication, risk factors (including dose-dependency), and quantification of risk for long-term consequences of CHOP or CHOP components as listed in Table 1. No dated restrictions were imposed but only publications in English or with an English abstract were included.

Studies meeting the inclusion criteria were retrieved in full. Data were collected using a focused data extraction form to systematically retrieve the data pertaining to relevant long-term consequences. Data were extracted and qualitatively synthesized where >3 studies were identified. Information of interest included study country(ies), chemotherapy regimen(s) received, patient population (cancer type; transplant yes/no), study features (design, N, type), long-term consequence-related outcomes of interest endpoints (definition and results).

Results

Description of retrieved articles

One hundred and seventy-three abstracts were retrieved from the COG LTFU guidelines and 61 articles qualified for data extraction (Figure 1). The majority of studies were based on research conducted in the United States of America (USA) and with multinational data; seven European Union (EU) countries provided 22 studies; more than half were from France ($n = 9$), the Netherlands ($n = 4$), and Norway ($n = 3$). Most studies were based on some form of retrospective analysis, cross-sectional analysis (11%), case-control study (8%), and longitudinal, prospective cohort studies (8%) accounted for 27% of the studies. Overall, 80% of studies were published since 2005 and 95% of studies included a pediatric patient population. Duration of follow-up was reported for the majority of studies (2– 26.5 years after cancer treatment), but few studies reported the time to actual development (onset) of complications. There was a wide range of incidence for most of the late effects, likely due to variations in treatment regimens, time period of measurement, and definition.

All studies included a mix of chemotherapies; over 50% of studies evaluated the late effects of anthracycline or alkylating agents; the late effects associated with corticosteroids were evaluated by 15% of studies. (Figure 2). None of the articles focused on the CHOP regimen specifically. Cardiac toxicity, hormone deficiencies, and infertility were well-described (14 studies each); therapy-related myelodysplasia (t-MDS) and acute myeloid leukemia (AML) were reported by seven studies; osteonecrosis was reported by six studies, and bladder malignancy and urotoxicity were reported in four studies. Seven studies included data on transplant recipients, all in HCT patients.

There was limited evidence (with ≤3 studies identified and insufficient data for meaningful synthesis) identified from the COG LTFU citations for several long-term adverse effects specifically for reduced bone mineral density, mental health disorders, socioeconomic issues, fatigue/sleep, dental abnormalities, Raynaud's phenomenon, neuropathy, cataract, and quality of life effects. These studies are not discussed in detail but limited evidence indicated links between increasing cumulative cyclophosphamide exposure and increased risk for dental abnormalities (in terms of significantly higher HDI scores and up to a 2-fold increase in dental health issues)[17,18], glucocorticoid exposure ≥5000 mg/m^2 and risks of reduced bone mineral density[19], and corticosteroid use with risk of somatization, anxiety, task efficiency, and

Table 1. Inclusion and Exclusion Criteria.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Endpoint criteria	
• Acute myeloid leukemia • Bladder malignancy • Cardiac toxicity • Cataracts • Clinical leukoencephalopathy • Dental abnormalities • Hepatic dysfunction • Impaired spermatogenesis • Myelodysplasia • Neurocognitive deficits • Osteonecrosis (avascular necrosis) • Ovarian hormone deficiencies • Pulmonary fibrosis • Pulmonary toxicity • Reduced bone mineral density (BMD) • Reduced ovarian follicular pool • Renal toxicity • Sinusoidal obstruction syndrome (SOS) • Urinary tract toxicity • Adverse psychosocial/quality of life effects • Mental health disorders • Fatigue • Sleep problems • Socioeconomic issues • Psychosocial disability due to pain • Peripheral sensory neuropathy	• Limitations in healthcare and insurance access • Ototoxicity • Risky behaviors (i.e. alcohol use)
Research concept-related criteria	
• Publications assessing long-term adverse events in the context of CHOP and its components	• Publications not assessing long-term adverse events in the context of CHOP and its components
Study countries and publication year	
• All	• All
Publication language	
• English; foreign language papers with English abstracts	• Foreign language publications
Publication type and study design	
• Randomized controlled trials ($n > 100$) • Observational study ($n > 100$) • Cross-sectional study ($n > 100$) • Systematic review • Case series ($n > 20$)	• News • Video-audio media • Webcast • Case reports • Case series ($n < 20$) • Letter • Commentary • Review • Treatment/practice guidelines • Consensus development • Note • RCT, observational study, or cross-sectional study with $n < 100$

memory difficulties[20]. Other (non-CHOP/CHOP component-related) potential risk factors identified included receipt of radiation (cataracts[21]) male gender, low BMI, and white race (low bone mineral density[19]), and cigarette smoking (Raynaud's phenomenon[22]).

Summary findings: Cardiac toxicities (14 studies) – Anthracyclines

Fourteen studies reporting information relating to cardiac toxicity were included. These studies addressed heart failure (five studies), cardiomyopathy (two studies), abnormal echocardiogram (two studies), valvular disease (three studies), artery disease (two studies) and structure and function disorders (three studies)[23–36]. Overall, the follow-up period reported by studies ranged from one year after treatment completion to 30 years after diagnosis of cancer but the time to development of cardiac toxicity was not reported, except for one study suggesting that echocardiogram abnormalities may become evident as early as one year after treatment (Table 2).

Eleven studies reported anthracycline (±) radiotherapy dose-dependent cardiac toxicity (of any type) with an elevated risk reported even at doses lower than 150 mg/m^2 (traditionally thought to be a safe dose range)[23–25,27–29,31–34,36]. More specifically, the hazard ratios for heart failure at $\circ a \leq 300$ to <400 mg/m^2 dose were reported to be 4.33 (95% CI: 1.73– 10.84) and 13.19 (95% CI: 9.04–19.25) for daunorubicin and doxorubicin, respectively[27]. Studies also reported significantly elevated risk of cardiac toxicity in patients with lymphoma treated with anthracyclines (e.g. with HR of up to 12.2 (95% CI: 5.2–28.2)[32]) compared with the sibling cohort[28,32] (Table 3). Other factors for increased risks of cardiac toxicity described by these studies include young age at exposure (patients <5 years of age vs. ≥ 5 years of age at exposure had a significantly higher risk of

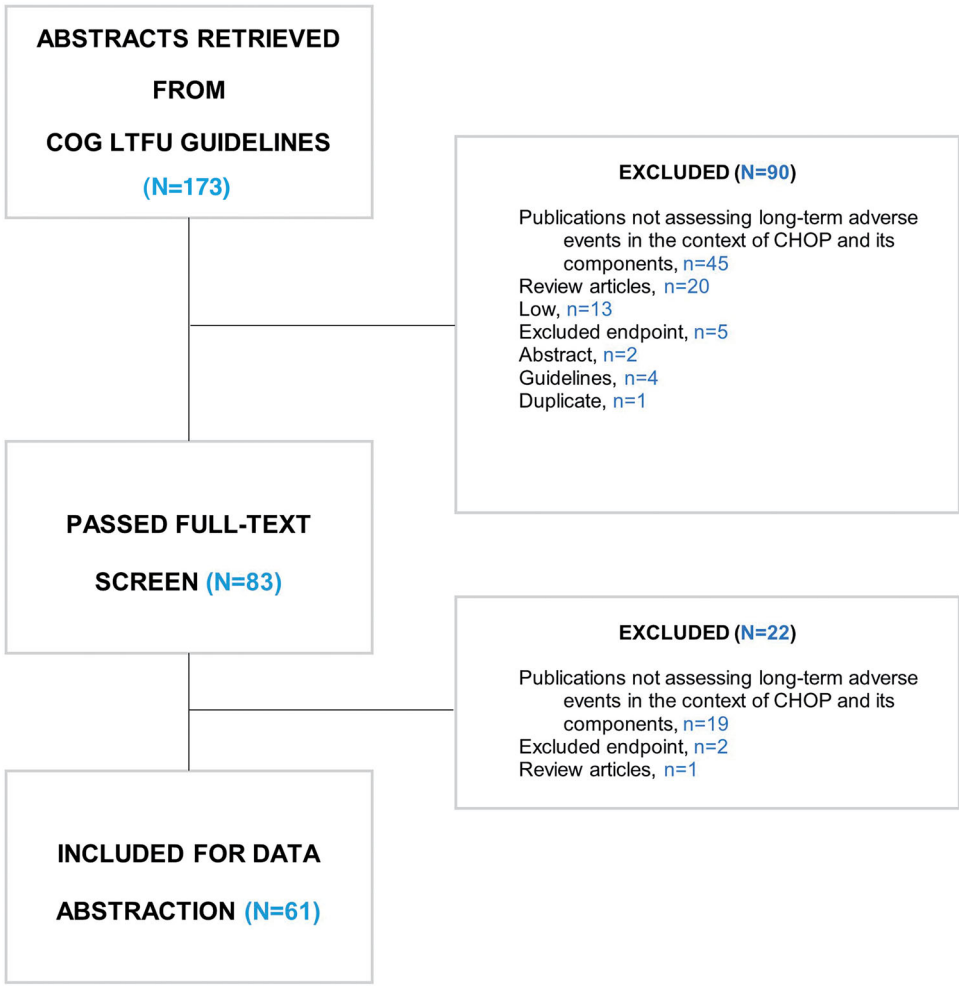

Figure 1. PRISMA Flowchart.

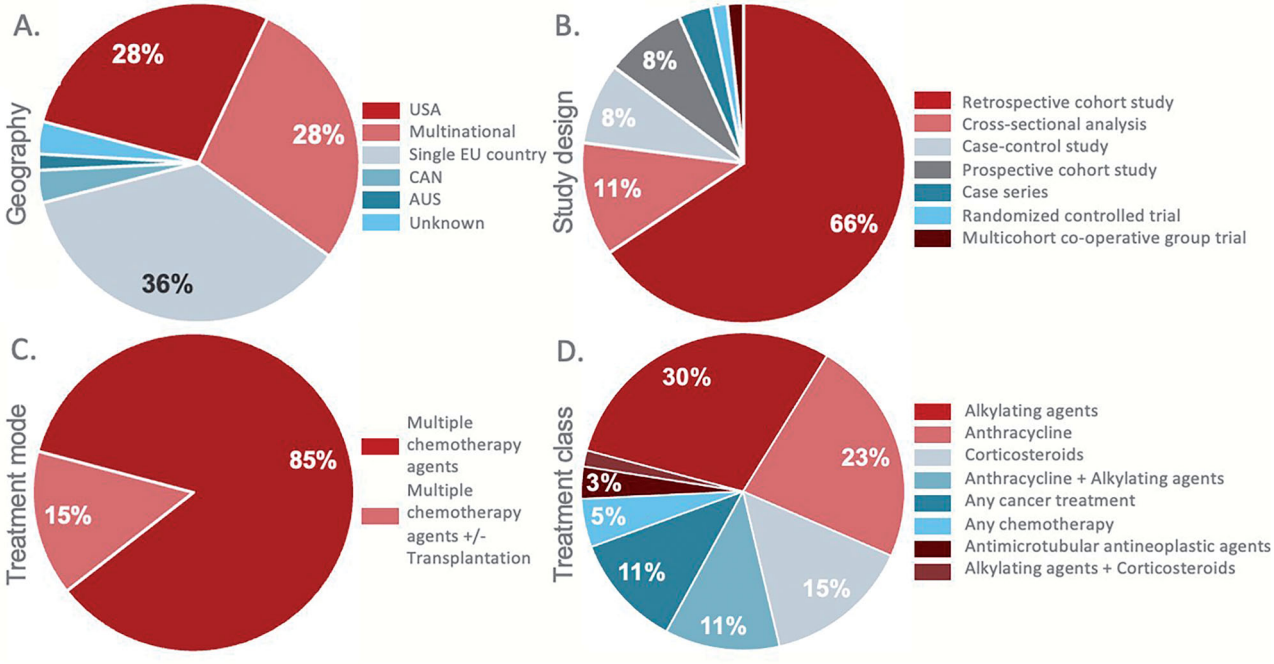

Figure 2. Characteristics of included studies.

Table 2. Results summary: overview of identified late effects, reported frequency, time to onset, and risk factors.

LATE EFFECTS (Number of studies)		DRUG CLASS	NUMBER OF PATIENTS IMPACTED	INCIDENCE/ PREVALENCE	TIME TO ONSET	RISK FACTORS
Cardiac toxicity ($N = 14$)	Heart failure	ATC	High	1.7% at 5 yrs* to 68.1% at 17.3 yrs^	NR	Dose, age, homozygous for the CBR3 V244M G allele, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, hypertension
	Abnormal echocardiogram	ATC	High	14.7% at 15.8 yrs* to 35% at 8 yrs*	1 yr*	
	Valvular disease	ATC	High	1.5% by 45 yrs of age to 28% at 22.6 yrs^	NR	
	Structure and function disorder	ATC	High	1.3% by 45 yrs of age to 48% at 28 yrs^	NR	
	Cardiomyopathy	ATC	Low	5% at 10 yrs^ to 7.4% at 22.6 yrs^	NR	
	Artery disease	ATC	Low	3.8% at 22.6 yrs^ to 5.3% by 45 yrs of age	NR	
Hormone deficiencies, infertility ($N = 14$)	Male	ALK	High	50% at 4.9 yrs* to 60% at 3.32 yrs*	NR	Dose, age, radiation use, Hodgkin's lymphoma, non-Hodgkin's lymohoma
	Female	ALK	High	7.6% NR to 83% at 4.9 yrs*	NR	
Secondary leukemia ($N = 7$)	t-MDS/AML	ATC ALK	Moderate	0.3% at 30 yrs* to 11% at 5 yrs*	2.6 to 4.4 yrs*	Dose, Hodgkin's lymphoma
Osteonecrosis ($N = 6$)	Avascular necrosis	CTS	Low	0.43% at 20 yrs* to 9.7% at 6 months^	1.8 to 2.4 yrs*	Dose, age, sex, Hodgkin's lymphoma, non-Hodgkin's lymphoma
Urotoxicity, bladder malignancy ($N = 4$)	Hemorrhagic cystitis	ALK	NR	NR	NR	Dose, radiotherapy
	Bladder cancer	ALK	Moderate	0.5% at 8.5yrs* to 10.7% at 12 yrs*	5 to 8.5 yrs*	

*=after treatment; ^=after diagnosis; AML, acute myeloid leukemia; ATC, anthracycline; AMT, antimicrotubular; ALK, alkylating agents; CTS, corticosteroids; NR, not reported; yr(s), years. High ≥20% of patients affected; Moderate = 10–20% of patients affected; Low ≤10% of patients affected.

cardiac toxicity (HR of 1.89 (95% CI: 1.08–3.31))[23,33]), the presence of hypertension[24], and homozygous for the CBR3 V244M G allele[26] (Table 3).

Summary findings: Hormone deficiencies and infertility (14 studies) – Alkylating agents

Overall, 14 studies were included reporting relevant data regarding hormone deficiencies and infertility[37–50]. Study follow-up ranged from 3 to 21 years following treatment but time to onset was not reported by any study (Table 2).

Hormone deficiencies, azoospermia, and oligospermia in male cancer survivors

Four studies reported prevalence of hormone deficiencies, azoospermia, and oligospermia in male cancer survivors exposed to alkylating agents; the prevalence of hormone deficiencies (such as abnormal follicle-stimulating hormone level and luteinizing hormone level) ranged from 50% to 60% but was based on few patients (only 5 and 12 survivors)[37,44,47,50]. Oligospermia was reported by only one study at 28%[44], azoospermia was reported by two studies with a range between 5.3% and 80%, with the highest prevalence reported in patients receiving cyclophosphamide ≥19 g/m^2 [44,47].

Hormone deficiencies and menopause/amenorrhea in female cancer survivors

Eight studies reported wide-ranging estimates for the prevalence of hormone deficiencies and amenorrhea in female cancer survivors exposed to alkylating agents, likely due to disparate definitions[37–39,44,46,48–50]. Five studies suggest that the prevalence of hormone deficiencies (abnormal follicle-stimulating hormone level and anti-Müllerian hormone level) ranged from 7.6% to 83%[37,45,46,49,50]. Three studies described the negative impact of cancer therapies on ovarian reserve[41,46,49], patients exposed to high-dose cyclophosphamide (>7.5 g/m^2) were at statistically significantly higher risk (odds ratio of 12.0 (95% CI: 1.3– 107.4)) for diminished ovarian reserve as measured by their anti-Müllerian hormone level[46].

Menopause/amenorrhea/ovarian failure (three studies) was estimated to affect between 8% and 67% of women[38,39,48]. The risk of ovarian failure and early menopause was shown to be associated with alkylating agent exposure[39], and dose-dependent with risks as much as 27-fold higher in patients treated with both radiation below the diaphragm and alkylating agent chemotherapy[38] (Table 3). Older age at treatment (13–20 years) further increased the risks associated with alkylating agents, as did type of primary cancer as, compared with survivors of other childhood cancers, patients diagnosed with Hodgkin's lymphoma, and Non-Hodgkin's lymphoma had a 3.8 (95% CI: 2.7–5.4) and 3.2 (95% CI: 1.8–5.3)-fold increase in risk of ovarian failure, respectively[39,48] (Table 3).

Childbearing

For both men and women, alkylating agent exposure was associated with a reduced likelihood of becoming pregnant or fathering a child; when compared with same sex siblings, the pregnancy rate dropped by 19% in women and by 44% in men[42,43] (Table 3). These affects were also found to be dose-dependent[40,42,43,45].

Table 3. Results summary: overview of selected quantitative comparative risks (expressed as HR, RR, RTR, OR) reported by identified studies.

CATEGORY	LATE EFFECTS	RISK FACTOR	TREATMENT CLASS	COMPARISON	DETAILS	REPORTED INCREASE IN RISKS Expressed as HR, RR, RTR, OR (95% CI)
Cardiac toxicity	Cardiac toxicity (including heart failure, myocardial infarction, pericardial disease, valvular abnormalities, abnormal echocardiogram)	Dose [27]	ATC	Heart failure in exposed cancer survivors	DAU $\leq$ 300 mg/m^2-<400 mg/m^2	HR 4.33 (1.73 to 10.84)
					DRN $\leq$ 300 mg/m^2-<400 mg/m^2	HR 13.19 (9.04 to 19.25)
		Primary cancer diagnosis [32]	ATC	Myocardial infarction in exposed Hodgkin's Lymphoma survivors vs. other tumors	Hodgkin's Lymphoma	HR 12.2 (5.2 to 28.2) $p < .001$
					Non-Hodgkin's Lymphoma	HR 2.9 (0.9 to 9.6) $p = .085$
		Age at treatment start [23]	ATC	Abnormal echocardiogram in younger vs. older exposed cancer survivors	Aged 1–4 years	HR 1.89 (1.08 to 3.31)
		CV risk factors [24]	ATC	Exposed cancer survivors with vs. without CV risk factors (diabetes, hypertension, dyslipidemia, obesity)	Hypertension	RTR 12.4 (7.6 to 20.1) $p < .001$
					Hypertension + dyslipidemia	RTR 11.3 (4.6 to 27.5) $p < .001$
					Hypertension + diabetes	RTR 16.9 (5.1 to 55.7) $p < .001$
					Hypertension + obesity	RTR 6.5 (2.5 to 16.5) $p < .001$
		Homozygous for the CBR3 V244M G allele	ATC	Exposed cancer survivors homozygous for G allele in CBR3 vs. unexposed patients with at least one copy of variant A allele in CBR3	1–100mg/m^2	OR 2.16 (0.47 to 10.05)
					301 + mg/m^2	OR 27.71 (7.42 to 103.44)
Hormone deficiencies, infertility	Diminished ovarian reserve (AMH level)	Dose [46]	ALK	Exposed vs. unexposed cancer survivors	CPS > 7.5 g/m^2	OR: 12.0 (1.3 to 107.4) $p = .03$
	Acute ovarian failure/ Early menopause	Drug exposure/age [38]	ALK	Exposed younger vs. unexposed older cancer survivors	Aged 21–25 yrs, ALK + RTb	RR: 27.39 (12.42 to 60.35) $p \leq .01$
		Age at diagnosis [39]	ALK	Older vs. younger exposed cancer survivors	13–20 years (vs. 0–12)	OR 1.8 (1.4 to 2.4) $p < .0001$
		Primary cancer diagnosis [39]	ALK	Hodgkin's and non-Hodgkin's Lymphoma survivors vs. other tumors	Hodgkin's Lymphoma	OR 3.8 (2.7 to 5.4) $p < .001$
					Non-Hodgkin's Lymphoma	OR 3.2 (1.8 to 5.3) $p < .001$
	Risk of pregnancy	Drug exposure [42,43]	ALK	Exposed cancer survivors vs. unexposed same sex siblings	Female	RR 0.81 (0.73 to 0.90) $p < .001$
					Male	RR 0.56 (0.49 to 0.63) $p < .001$
Secondary leukemia	t-MDS/AML	Dose [52]	ALK	High dose vs. low dose treatment	DRN 450mg/m^2 + CPS 17.6g/m^2 + IFO 140g/m^2	RR 15.91 (3.84 to 65.82)
		Dose [51]	ALK	High dose vs. low dose treatment	ALK $\geq$ 10g/m^2	RR 6.2 (2.4 to 16.1) $p = .00001$
			ATC		ATC $\geq$ 0.2g/m^2	RR 1.6 (0.7 to 4.0) $p = .103$
		Primary cancer diagnosis [51]	ALK ATC	Exposed Hodgkin's Lymphoma survivors vs. other tumors	Hodgkin's Lymphoma	OR 2.0 (0.6 to 6.6) $p = .525$
		Primary cancer diagnosis [56]	ALK ATC	Exposed Hodgkin's Lymphoma survivors vs. other tumors	Hodgkin's Lymphoma	RR 6.4 (1.6 to 24) $p = .004$

(*continued*)

Table 3. Continued.

CATEGORY	LATE EFFECTS	RISK FACTOR	TREATMENT CLASS	COMPARISON	DETAILS	REPORTED INCREASE IN RISKS Expressed as HR, RR, RTR, OR (95% CI)
Osteonecrosis	Osteonecrosis	Drug exposure [60]	CTS ± RT/SG	Exposed cancer survivors vs. unexposed siblings	Chemotherapy including CTS ± RT/SG	RTR 6.2 (2.3 to 17.2)
		Drug exposure [60]	CTS	Exposed cancer survivors vs. unexposed siblings	DEX ± PRN	RTR 4.0 (1.8 to 8.9) $p < .001$
		Age at diagnosis [59]	CTS	Older vs. younger exposed cancer survivors	Aged ≥ 10 years	OR 5.52 (4.7 to 6.5) $p < .0001$
		Sex [63]	CTS	Female vs. male exposed cancer survivors	Females	OR 2.23 (1.04 to 4.81) $p = .04$
		Primary cancer diagnosis [60]	CTS	Exposed Hodgkin's and Non-Hodgkin's lymphoma survivors vs. unexposed siblings	Hodgkin's Lymphoma Non-Hodgkin's Lymphoma	RTR 6.7 (2.0 to 22.2) $p = .002$ RTR 6.7 (1.8 to 25.1) $p = .005$
Urotoxicity, bladder malignancy	Bladder cancer	Dose [67]	ALK	Exposed vs. unexposed cancer survivors	CPS 20–49 g CPS ≥ 50 g	MRR 6.3 (1.3 to 2.9) MRR 14.5 (2.3 to 94)
		Duration of exposure [67]	ALK	Exposed vs. unexposed cancer survivors	CPS 1–2 years CPS ≥ 2 years	MRR 3.7 (0.6 to 22) MRR 11.88 (2.3 to 61)

ATC: anthracycline; ALK: alkylating agents; AMH: Anti-Müllerian hormone; CI: confidence intervals; CTS: corticosteroids; CV: cardiovascular; CPS: cyclophosphamide; DAU: daunorubicin; DEX: dexamethasone; DRN: doxorubicin; HR: hazard ratio; IFO: ifosfamide; MRR: matched relative risk; OR: odds ratio; PRN: prednisone; RR: relative risk; RTb: radiation below the diaphragm; RTR: rate ratio; SG: surgery; vs.: versus.

Summary findings: Therapy-related myelodysplasia (t-MDS) and acute myeloid leukemia (AML) (seven studies) – Anthracycline and alkylating agents

Data for secondary leukemia known as t-MDS/AML were reported in seven studies with a maximum follow-up of 26.5 years following diagnosis[51–57]. The proportion of patients that developed t-MDS/AML was reported by five studies and ranged from 0.3% (at 30 years after treatment) to 11% (at five years after treatment) (Table 2). The median interval between treatment for first tumor to diagnosis of t-MDS/AML was reported by four studies ranging from 31 months to 4.4 years. Although the median interval between treatment for first tumor to diagnosis of secondary leukemia was <5 years, patients were found to be at significant risk of developing secondary leukemia well beyond 15 years from initial treatment[57].

Higher doses were associated with increased risk with patients exposed to high-dose doxorubicin (450 mg/m^2), cyclophosphamide (17.6 g/m^2), and ifosfamide (140 g/m^2) at a much greater risk (up to 16 (95% CI: 3.84– 65.82)-fold increase) compared with doxorubicin (375 mg/m^2) and cyclophosphamide (20.4 g/m^2)[52]; the high-dose category (≥10 g/m^2) of the alkylating agents was also associated with a 6.2 (95% CI: 2.4–16.1)-fold increased secondary leukemia risk compared with no exposure[51] (Table 3). Risks were also increased in patients with a primary cancer diagnosis of Hodgkin's lymphoma (2 (95% CI: 0.6– 6.6) to 6.4 (95% CI: 1.6–24)-fold greater risk)[51,56] (Table 3).

Summary findings: Osteonecrosis (six studies) – Corticosteroids

Overall, six studies were included with a maximum follow-up of almost 12 years after treatment[58–63]. Five studies reported the percentage of patients developing osteonecrosis after cancer treatment ranging from 0.43% (at 20 years after treatment) to 9.7% (6 months after diagnosis) (Table 2). Onset was reported to be within four years from treatment initiation with median ranging from 1.8 years to 2.4 years. The risk of osteonecrosis was higher in patients exposed to higher doses of corticosteroids (as part of an intensive regimen[59]) with one study showing cancer survivors had a 6.2 (95% CI: 2.3–17.2) times higher likelihood of osteonecrosis as compared with their sibling comparison group with exposure to glucocorticoid therapy being a major risk factor[60] (Table 3). The risk of osteonecrosis was also consistently higher in children of older age (>10 years), female gender, and a history lymphoma[58,59,61–63] (Table 3).

Summary findings: Bladder malignancy and urotoxicity (four studies) – alkylating agents

Four studies were included, notably these studies were older with all four pre-dating 1998[64–67]. Three studies reported the prevalence of bladder cancer[64,65,67] and three studies described hemorrhagic cystitis in cancer patients that were exposed to cyclophosphamide[64–66] (Table 2). The onset of

bladder cancer following cancer treatment ranged from 5 to 8.5 years (the duration of follow-up in identified studies ranged from 4 to 17 years). The risk of bladder cancer significantly increased with increasing dose of cyclophosphamide, with a 6 (95% CI: 1.3–2.9) and 14.5 (95% CI: 2.3–94)-fold increased risk at cumulative doses of 20–49 g and ≥50 g, respectively; risks also increased with duration of treatment with a 3.7 (95% CI: 0.6–22)-fold and 11.8 (95% CI: 2.3–61)-fold increased risk for 1–2 years and ≥2 years of treatment[67] (Table 3).

Summary findings: Transplant recipients (seven studies) – Alkylating agents and corticosteroids

A total of seven studies with transplant patients were identified, all of which evaluated children, adolescent, or young adult patients with HCT. None of the studies assessed solid organ transplant (SOT) and none of the studies focused specifically on the CHOP regimen or PTLD[37,41,46,49,59,60,68]. The reported long-term consequences of alkylating agents (e.g. cyclophosphamide) and corticosteroids as primary treatment in patients with HCT included hormone deficiencies and infertility ($n = 4$ studies), osteonecrosis ($n = 2$), and health status and quality of life assessed using SF-36 questionnaire ($n = 1$).

Hormone deficiencies (four studies)

Cancer survivors who received alkylating agents experienced hormone deficiencies and those with a HCT were at increased risk; compared with cancer survivors (CS) without a history of HCT, cancer survivors with a history of HCT (CS-HCT) and a history of total body irradiation had significantly impaired follicle stimulating hormone, estradiol, inhibin B, anti-Müllerian hormone, antral follicle count, and ovarian volume[37,41,46,49].

Osteonecrosis (two studies)

CS-HCT patients also had a significantly increased risk of developing osteonecrosis compared with the CS group treated with chemotherapy (6.8% vs. 1.4%), patients developed symptomatic osteonecrosis within a median of 2.4 years in the CS group with chemotherapy and 0.9 years after first transplant in the CS-HCT group[59]; rates were highest among the CS-HCT for acute lymphoblastic leukemia, acute myelogenous leukemia, and chronic myelogenous leukemia[60].

Quality of life (one study)

Childhood acute leukemia survivors treated with HCT with preparative regimen with either busulfan-cyclophosphamide or total body irradiation/cyclophosphamide had a significantly lower QoL short-form (SF)-36 mental and physical composite scores compared with norms[68].

Results suggest that immunocompromised HCT recipients who were childhood cancer survivors were significantly more impaired by long-term consequences (specifically hormone deficiencies and infertility, osteonecrosis, and QoL) following primary treatment with alkylating agents and corticosteroids compared with other matched CS without HCT.

Discussion

For patients exposed to anthracycline, alkylating agents, and corticosteroids as part of their cancer therapy, there is consistent evidence of a significant dose-dependent risk of cardiac toxicity, hormone deficiencies and infertility, t-MDS/AML, osteonecrosis, and bladder cancer. These effects are significant, impact a high percentage of patients, and occur as early as one year after treatment. Cardiac toxicity was seen to impact a notably high proportion of patients treated with anthracycline, with heart failure reported to affect up to 68% of patients and structure and function disorders up to 48%. These effects were seen from as early as one year to as late as 28 years after receiving a primary cancer diagnosis. Hormone deficiencies also impacted a high proportion of patients, affecting up to 60% of male and 83% of female patients at three to five years after treatment with alkylating agents. Significant adverse effects on fertility and lasting reproductive risks were also evident. T-MDS/AML, osteonecrosis, and bladder cancer affected fewer patients (up to 9.7%–11%) but risks persisted over time and were still increased at 20–30 years following treatment.

Although none of the studies focused specifically on the CHOP regimen, 30%, 23%, and 15% evaluated alkylating agents (e.g. cyclophosphamide), anthracyclines (e.g. doxorubicin), and corticosteroids (e.g. prednisone), respectively. All three product classes had a dose-dependent risk of long-term consequences with notably increased risk of heart failure (increased up to 13.19 (95% CI: 9.04–19.25) fold), early menopause (increased up to 27-fold), secondary leukemia (increased up to 15.91 (95% CI: 3.84– 65.82)-fold), bladder cancer (increased up to 14.5 (95% CI: 2.3– 94) fold), and osteonecrosis (increased up to 6.2 (95% CI: 2.3–17.2) fold). More specifically, surviving Hodgkin's and non-Hodgkin's lymphoma patients had significantly elevated risk of cardiac toxicity (up to 12.2 (95% CI: 5.2–28.2) fold increase), ovarian failure (up to 3.8 (95% CI: 2.7–5.4) fold increase), and osteonecrosis (up to 6.7 (95% CI: 2.0–22.2) fold increase). No studies were found in PTLD or SOT, highlighting the acute need for future research in this area. Other key risk factors persistently associated with late effects include age, gender, primary cancer diagnosis, and radiation exposure. These factors go some way in helping to establish which cancer patients might benefit most from extended follow-up and/or ongoing screening following treatment with CHOP or one of its components. Other long-term consequences were identified in the COG LTFU (reduced bone mineral density, mental health disorders, socioeconomic issues, fatigue/sleep, dental abnormalities, Raynaud's phenomenon, neuropathy, cataract, and quality of life effects), but were not supported by sufficient articles to synthesize. These potential effects may warrant further investigation and a systematic literature search may provide additional data and permit quantification.

Although the long-term adverse consequences of CHOP are known and other publications identify these issues, this

review focuses on the quantification (e.g. magnitude, time to onset of the effects, and relationship to other factors) in children or young adults from the COG LTFU (where these consequences can be observed over a longer follow-up period). Uniquely, this review also set out to evaluate CHOP-related risks specifically for PTLD patients (though, as anticipated, no relevant data was found) and consequently provides only an overview of risks for HCT recipients as well as across different cancer types. Based on this comprehensive quantification, a better understanding of the risks associated with the components of CHOP should help facilitate more informed treatment decisions and reduce the overall burden of long-term consequences on patients.

Study limitations

Our approach to the studies identified in this review was pragmatic and we did not aim to perform quality appraisal for selected studies; there was considerable heterogeneity in methodological approaches, target populations, study time frames, and perspectives. Furthermore, this review was not a systematic literature review and de novo systematic searches were not undertaken. Although the COG LTFU represent a comprehensive resource, it is possible that relevant studies were overlooked or have been published since the last COG LTFU update in 2018.

Only limited evidence (<3 studies) that could not be synthesized was identified from the COG LTFU for several long-term consequences of CHOP components (reduced bone mineral density, mental health disorders, socioeconomic issues, fatigue/sleep, dental abnormalities, Raynaud's phenomenon, neuropathy, cataract, and quality of life effects). No studies were found that specifically addressed the CHOP regimen. In addition, the studies included in this review were drawn from COG LFTU which is focused on a pediatric population with 95% of studies focused on childhood cancers. There may be differences between adults and children in terms of the tolerability of chemotherapy, with adults potentially worse affected in some circumstances[69], which may limit the applicability of the results of this review. Finally, the long-term consequences may not be established in diseases with short survival.

Conclusions

Patients exposed to components of CHOP have a dose-dependent risk of cardiac toxicity, infertility, secondary leukemia, osteonecrosis, and bladder cancer that are often significant, impact a high percentage of patients, and occurred as early as one year after treatment. Some complications from chemotherapy are more common in transplant recipients due to long-standing immunosuppression and the available evidence suggests that immunocompromised HCT patients may be significantly more impaired by hormone deficiencies and infertility, osteonecrosis, and poorer QoL. However, since only a small number of studies of long-term consequences in transplant recipients were identified and no studies were seen in patients with PTLD or in SOT patients, more research is needed to evaluate long-term adverse consequences of CHOP or its components in these patient groups. Safe and effective PTLD treatments that potentially avoid these long-term consequences of chemotherapy are urgently needed.

Transparency

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Conception and design, or analysis and interpretation of the data (all authors); the drafting of the paper or revising it critically for intellectual content (all authors); the final approval of the version to be published (all authors). All authors agree to be accountable for all aspects of the work.

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Previous presentations

Watson C, Gadikota H, Barlev A, et al. A Review of the Risks of Long-term Consequences Associated with Components of CHOP Chemotherapy Regimen. Poster ID #112602 presented at ISPOR EU 2021

Watson C, Gadikota H, Barely A, et al. Quantification of Long-Term Consequences Associated with Components of the CHOP Chemotherapy Regimen. Poster ID 4589 presented at ASH 2021

Watson C, Gadikota H, Barlev A, et al. An Evidence Review of the Long-Term Consequences Associated with Components of the CHOP Chemotherapy Regimen in Transplant Recipients. Poster ID 4586 presented at ASH 2021.

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