A Review of the Risks of Long-term Consequences Associated with Components of CHOP Chemotherapy Regimen

POSB172

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Background

- A common chemotherapy regimen in Epstein-Barr virus-associated post-transplant lymphoproliferative disease (EBV+ PTLD) following solid organ transplants is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)
- The Children's Oncology Group Long-term Follow-up (COG LTFU) guidelines[1] was developed to increase awareness and provide recommendations for screening/management of long-term consequences, defined as therapy-related complications that persist or arise after treatment, in survivors of pediatric malignancies based on risk and exposure of therapies, including chemotherapies
  - These long-term treatment consequences are not quantified in the guidelines

Objective

- This study describes the long-term treatment-related consequences relating to the CHOP regimen in cancer survivors from the evidence in the COG LTFU guidelines

Methods

- The review was planned to build upon the evidence already identified by the COG LTFU guidelines[1], these guidelines represent a comprehensive source of relevant information making additional de novo searches of limited incremental value
- An Excel database was developed containing abstracts for 14 potential long-term consequences of CHOP or CHOP components identified from the COG LTFU guideline references; these abstracts were screened against pre-specified inclusion and exclusion criteria
- Eligibility was based upon reporting data for one or more long-term complication of interest along with pre-specified criteria:
  - Identified long-term consequences: cardiac toxicity, hormone deficiencies/fertility, AML, osteonecrosis, urotoxicity and bladder malignancy, dental abnormalities, mental health disorders, fatigue/sleep, health status and QoL, peripheral sensory or motor neuropathy, reduced BMD, socioeconomics, cataracts, Raynaud's phenomenon
  - English or English language abstract across all publication years
  - Study design: systematic review, RCT (n>100), observation study (n>100), cross-sectional study (n>100), case series (n>20)
- 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 endpoints (definition and results) including incidence/prevalence, time to development of complication (onset), risk factors (including dose-dependency)

Results

- Of the 173 abstracts retrieved, 61 studies were included (**Figure 1**), 66% were retrospective cohort studies, 28% were in the USA, 36% were in the EU (**Figure 2**)

Figure 1. PRISMA Flowchart

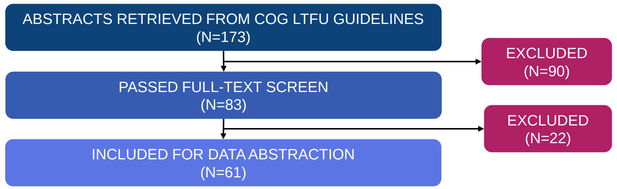
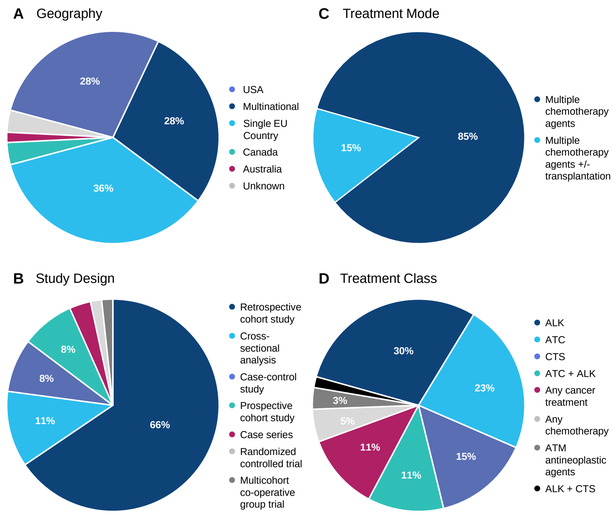


Figure 2. Characteristics of Included Studies (N=61)



- 95% of studies were in the pediatric population
- No study focused specifically on the CHOP regimen; seven studies addressed transplant recipients
- Long-term consequences of components of CHOP observed in >3 studies included cardiac toxicity (n=14), hormone deficiencies or infertility (n=14), acute myeloid leukemia (n=7), osteonecrosis (n=6), and urotoxicity/ bladder malignancy (n=4) (**Table 1**)
- 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
- 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 (**Table 1**)
- The synthesized evidence shows a dose-dependent risk of these long-term consequences amongst all three drug classes (anthracycline, alkylating, and corticosteroid agents); other key risk factors included age, sex, primary cancer diagnosis, and radiation usage (**Table 1**)

Table 1. Long-term Consequences of CHOP Observed in >3 Studies

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, primary cancer diagnosis, 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, (Non)Hodgkin's lymphoma
	Female	ALK	High	7.6% NR to 83% at 4.9 yrs*	NR	
AML (N=7)	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
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; **High** = >20% of patients affected; **Moderate** = 10-20% of patients affected; **Low** = <10% of patients affected

Limitations

- De novo systematic searches were not undertaken and 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 for several long-term consequences of CHOP components
  - Dental abnormalities
  - Mental health disorders
  - Fatigue/sleep
  - Health status and quality of life effects
  - Peripheral sensory or motor neuropathy
  - Reduced bone mineral density
  - Socioeconomic issues
  - Cataracts
  - Raynaud's phenomenon
- No data was found specifically on the CHOP regimen
- Studies focused on pediatric malignancies and may not be generalizable to all cancers or populations
- Long-term consequences data may be limited in diseases with short survival

Conclusions

- **Cancer survivors initially exposed to anthracycline, alkylating, or corticosteroid agents 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 occur as early as 1 year after treatment**
- **Since only a small number of studies of late effects were identified in hemopoietic stem cell transplant recipients and none were seen in patients with EBV+ PTLD or in SOT recipients, more research is needed to evaluate adverse consequences of CHOP or its components in EBV+ PTLD following SOT**
- **Safe and effective EBV+ PTLD treatments that avoid these potential long-term consequences of CHOP are urgently needed**

References

COG LTFU; Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, Version 5.0, Oct 2018, http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf

Disclosures

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Abbreviations

AML=acute myeloid leukemia; **ATC**=anthracycline; **AMT**=antimicrotubular; **ALK**=alkylating agents; **BMD**=bone mineral density; **CTS**=corticosteroids; **NR**=not reported; **QoL**=quality of life; **RCT**=randomized controlled trial; **yr(s)**=years

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