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Peripheral Neuropathy Incidence in Children, Adolescents and Young Adults with Cancer and Medicaid Insurance in California

Renata Abrahão, MD, MSc, PhD¹, Julianne J.P. Cooley, MS², Justine M. Kahn, MD, MS³, Ann Brunson, MS¹, Elysia M. Alvarez, MD, MPH⁴, Anjlee Mahajan, MD⁵, Ted Wun, MD^{1,2}, Rashmi Verma, MD⁵, Kathryn J. Ruddy, MD, MPH⁶, Theresa H.M. Keegan, PhD, MS^{1,2}

¹. Center for Oncology Hematology Outcomes Research and Training (COHORT), Division of Hematology and Oncology, University of California Davis Comprehensive Cancer Center, Sacramento, CA

². California Cancer Reporting and Epidemiologic Surveillance Program, University of California Davis Comprehensive Cancer Center, Sacramento, CA

³. Department of Pediatrics, Columbia University Medical Center, New York, NY

⁴. Department of Pediatrics, Division of Pediatric Hematology and Oncology, University of California Davis School of Medicine, Sacramento, CA

⁵. Division of Hematology and Oncology, University of California Davis Comprehensive Cancer Center, Sacramento, CA

⁶. Department of Oncology, Mayo Clinic, Rochester, MN

Abstract

Background: Chemotherapy-induced peripheral neuropathy is a potentially debilitating adverse effect of cancer therapy that can lead to delay, reduction or discontinuation of cancer treatment. Population-based data on peripheral neuropathy incidence among young cancer survivors is lacking.

Methods: Using a linkage between Medicaid, the California Cancer Registry, hospitalization and emergency department data, we identified 6,028 adolescents and young adults (15–39 years) with Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), breast, colorectal or testicular cancer and 418 children (<15 years) with HL or NHL during 2005–2017. We determined the cumulative

Corresponding author Renata Abrahão, MD, MSc, PhD, Division of Hematology and Oncology, UC Davis Comprehensive Cancer Center, 4501 X Street, Suite 3016 Sacramento, California 95817, rabrahao@ucdavis.edu.

Authors contributions

Conceptualization and methodology: RA, TK, JMK

Formal analysis: JC, AB

Supervision: RA, TK

Writing (original draft): RA

Writing (review and editing): All authors

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incidence of peripheral neuropathy and its association with neurotoxic chemotherapy identified from Medicaid claims, using multivariable Cox proportional hazards regression models.

Results: Of 6,446 patients, 1007 were diagnosed with peripheral neuropathy. Across each cancer type, incidence was higher among patients receiving neurotoxic drugs. For example, compared with non-neurotoxic agents, five-year cumulative incidence was higher with oxaliplatin for colorectal (24.0% vs 6.2%) and paclitaxel for breast cancer (22.6% vs. 5.1%). In multivariable analysis, the agents most strongly associated with peripheral neuropathy were brentuximab (+/- other neurotoxic drugs) for HL (Hazard Ratio (HR)=9.5, 95% confidence interval (CI) 5.95–15.26), brentuximab (+/-vinca alkaloids, HR=7.0, CI 4.13–11.87) for NHL, paclitaxel for breast (HR=4.0, CI 3.05–5.31); oxaliplatin for colorectal (HR=3.5, CI 2.23–5.36), and cisplatin and etoposide for testicular cancer (HR=2.1, CI 1.37–3.11).

Conclusions: The high incidence of peripheral neuropathy highlights the need for frequent monitoring, new supportive care approaches, and development of novel therapeutic agents to minimize toxicity while maintaining treatment efficacy.

Keywords

Peripheral neuropathy; chemotherapy; cancer; children; adolescents and young adults; Medicaid

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and potentially debilitating adverse effect of cancer treatment, often resulting in treatment delay, interruption or dose modifications, which can negatively impact cancer outcomes.¹ CIPN incidence varies widely, ranging from about 10% to over 80%,^{2–4} based on several factors, including the cumulative dose of neurotoxic agents, drug combinations, treatment duration, follow-up time, the presence of comorbidities (e.g., diabetes) and lifestyle factors (e.g., smoking and alcohol use).^{2,4,5}

Cytotoxic agents commonly associated with CIPN include taxanes, vinca alkaloids, platinum agents, brentuximab vedotin, bortezomib, and eribulin.^{1,6} According to a systematic review and meta-analysis involving over 4000 patients with cancer who received chemotherapy of any type, approximately 70% developed peripheral neuropathy by one month following the end of chemotherapy. Moreover, at six months or beyond, about 30% of patients were experiencing persistent peripheral neuropathy symptoms, leading to impairment of the quality of life of these patients.²

Existing data on CIPN in the United States (US) predominantly stem from clinical trials with small sample sizes and studies of older adult cancer survivors.^{7–11} There are limited population-based data on the incidence of CIPN and its association with specific chemotherapy drugs among pediatric (<15 years) and adolescent and young adult (AYA, 15–39 years) cancer survivors.^{12–15} To address this gap, we investigated peripheral neuropathy in children and AYAs with Medicaid insurance in California. For five common malignancies, we determined the cumulative incidence of peripheral neuropathy and the association of this

condition with neurotoxic and non-neurotoxic agents adjusting for sociodemographic and clinical factors.

Methods

Data Sources

We utilized data from the California Medicaid program linked to the California Cancer Registry (CCR), and to statewide hospitalization and emergency department data from the Department of Health Care Access and Information (HCAI). Data linkages were done through deterministic and/or probabilistic algorithms.¹⁶ Medicaid claims provide information on therapeutic agents and medical conditions not routinely available in cancer registries. Medicaid provides healthcare services for individuals with family income up to 138% of the poverty line, and also covers specific diseases, such as cancer.¹⁷ The CCR captures over 99% of cancer diagnoses in the state, providing information on tumor characteristics, patient demographics, and clinical data.¹⁸ HCAI data comprises hospital discharge data from all non-federal hospitals in the state. It provides information on up to 25 diagnoses, and up to 21 clinical procedures during each encounter.¹⁹

Participants

We included AYAs aged 15–39 years diagnosed with a first primary Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and invasive female breast, colorectal or testicular cancer from 2005 to 2017 (Figure 1). The selection of these cancers was based on their high incidence in AYAs and treatment protocols involving chemotherapy drugs known for their neurotoxic effects. We also included children <15 years with HL and NHL. Tumor primary site and histology codes were assigned based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).²⁰ AYA cancers were categorized according to new classification system proposed by Barr et al. 2020²¹ and HL and NHL were classified according to the International Classification of Childhood Cancer Recode ICD-0–3.²² Patients' inclusion and exclusion criteria are described in Figure 1. Our analysis required Medicaid enrollment with breaks of less than one month during the first 12 months following cancer diagnosis, corresponding to the period when patients typically receive most of their chemotherapy treatment.

Classification of Chemotherapy Drugs and Peripheral Neuropathy

From Medicaid claims, we classified neurotoxic drugs based on previous studies.^{1,6,9,11,23–25} These drugs were identified by multiple codes for each drug available in the US Food and Drug Administration (FDA) National Drug Codes (NDC) database²⁶ and in the Surveillance, Epidemiology, and End Result (SEER) Program website, which provides information on NDC and Healthcare Common Procedure Coding System (HCPCS).²⁷ We identified additional codes in medical websites as described in Supplemental Tables S1 and S2. The neurotoxic drugs identified were then classified into mutually exclusive cancer-specific categories based on clinical relevance.^{1,9,11,25} These drugs include taxanes (paclitaxel and docetaxel), vinca alkaloids (vincristine, vinblastine, and vinorelbine), platinum (oxaliplatin, carboplatin, and cisplatin), and other drugs (eribulin, etoposide, ixabepilone, brentuximab, bortezomib vedotin, and trastuzumab emtansine). Emtansine and vedotin are the neurotoxic

components in the latter drugs. We considered these drugs as being administered at any time during treatment. Patients who did not receive them were categorized as receiving non-neurotoxic drugs.

Using Medicaid and HCAI data, we selected the first ICD-9 or ICD-10 code recorded for peripheral neuropathy. We allowed multiple codes, including those not specific to drug-induced neuropathy. Supplemental Table S3 shows the distribution of codes.

Sociodemographic and Clinical Characteristics

From the CCR, we obtained information on age at diagnosis, sex, race/ethnicity, neighborhood socioeconomic status (nSES), stage at diagnosis, and cancer type. Race/ethnicity was categorized as non-Hispanic (NH) White, NH Black/African American (AA), Hispanic, Asian/Pacific Islander (PI), and other/unknown. Neighborhood SES (nSES) is an aggregated measure of seven indicators, including education, poverty, and unemployment rates at the census block-group level,²⁸ and it was classified in lowest, middle or highest. Stage at diagnosis was defined according to the American Joint Committee on Cancer (AJCC) classification and categorized into non-metastatic (stages I–III) and metastatic (stage IV) diseases. Given the increased risk of peripheral neuropathy among patients with diabetes,^{1,5,8} we collected information on diabetes history up to 5 years prior to cancer diagnosis using ICD-9 and ICD-10 diagnosis codes in HCAI, as done previously.²⁹

Statistical Analysis

Descriptive analyses show the distribution of patient's characteristics, both overall and by the presence or absence of peripheral neuropathy. Patients were followed from cancer diagnosis until diagnosis of peripheral neuropathy, death, date of last follow-up, or study endpoint (12/31/2019), whichever occurred first. Cumulative incidence of peripheral neuropathy along with corresponding 95% confidence intervals (CIs), were estimated using nonparametric models that accounted for death as a competing risk.³⁰

We used multivariable Cox proportional hazards regression to investigate the association between chemotherapy agents and peripheral neuropathy by cancer type. The multivariable models were adjusted for known risk factors and relevant sociodemographic and clinical variables,^{1,31,32} including age at diagnosis, sex, stage at diagnosis, history of diabetes, race/ethnicity, and nSES. Hazard ratios (HR) are reported with corresponding 95% CIs. The proportional hazard assumption was assessed using the Schoenfeld residuals test, with any covariates found to violate the assumption included as stratification variables in the models. All p-values were two-sided, with results deemed statistically significant at $p < 0.05$. All analyses were done using SAS/STAT[®] software version 9.4. This study was approved by the California Committee for the Protection of Human Subjects and the Institute Review Board of the University of California Davis.

Results

A total of 6,446 cancer survivors (418 children and 6028 AYAs) covered by Medicaid insurance were included in our study. During a median follow-up time of 4.8 years (interquartile range 2.7, 8.1), 1007 were diagnosed with peripheral neuropathy. The median

time from cancer diagnosis to peripheral neuropathy onset varied from 8 months for NHL, 13 months for colorectal and testicular cancer, and 21 months for HL and breast cancer. Most patients were female (60%), resided in the lowest socioeconomic neighborhoods (53%), were identified as Hispanics (57%), and received neurotoxic chemotherapy (55%) (Table 1). Approximately 5% of patients had a history of diabetes. Among patients diagnosed with peripheral neuropathy, 71.5% received neurotoxic drugs, while 28.5% received non-neurotoxic chemotherapy.

Cumulative Incidence of Peripheral Neuropathy

Across all cancers, peripheral neuropathy incidence was higher among patients who received neurotoxic chemotherapy (Table 2). Among patients with HL, 5-year cumulative incidence of peripheral neuropathy was 33.2% in patients receiving brentuximab, 13.1% in those receiving vinca alkaloids plus etoposide, and 12.8% in patients receiving vinca alkaloids as a sole neurotoxic drug, compared to 3.0% in patients treated with non-neurotoxic chemotherapy. Among patients with NHL, 5-year peripheral neuropathy cumulative incidence was 70.3% among patients receiving brentuximab, 20.3% in those receiving vinca alkaloids as sole neurotoxic drug, and 18.5% in patients who received vinca alkaloids plus etoposide, compared to 11.4% among those receiving non-neurotoxic drugs. In patients with breast cancer, the highest 5-year peripheral neuropathy cumulative incidence was observed among patients receiving paclitaxel (22.6%), followed by paclitaxel plus carboplatin (20.8%), and docetaxel plus carboplatin (18.0%), compared to 5.1% in those receiving non-neurotoxic chemotherapy. Among patients with colorectal cancer, 5-year peripheral neuropathy cumulative incidence was 24.0% among AYAs receiving oxaliplatin compared to 6.2% in those receiving non-neurotoxic drugs. Among patients with testicular cancer, 5-year cumulative incidence of peripheral neuropathy was 16.6% in patients receiving cisplatin plus etoposide, compared to 7.6% in those receiving non-neurotoxic regimens.

The incidence of peripheral neuropathy increased over time across all cancer sites and chemotherapy regimens. In patients with Hodgkin lymphoma, for instance, the cumulative incidence for those receiving vinca alkaloids increased from 6.85% at 1 year to 12.81% at 5 years, and for those treated with brentuximab, it rose from 8.62% at 1 year to 33.22% at 5 years. Similar increasing trends were observed across other cancer sites, particularly among patients receiving neurotoxic chemotherapy regimens. For patients treated with non-neurotoxic drugs, the cumulative incidence also increased over time, but to a lesser extent. These trends are summarized in Table 2.

Multivariable-Adjusted Associations of Chemotherapy Agents with Peripheral Neuropathy

In multivariable models, the hazard of peripheral neuropathy varied by cancer site, with patients who received neurotoxic chemotherapy experiencing 1.7 to 9.5 times higher hazards compared to those treated with non-neurotoxic drugs (Table 3). Among patients with HL, brentuximab, either alone or in combination with other neurotoxic drugs (9.9%), exhibited the strongest association with peripheral neuropathy (HR=9.53, CI 5.95–15.26), followed by vinca alkaloids plus etoposide (HR=4.43, CI 2.34–8.41) and vinca alkaloids alone (3.19, CI 2.08–4.89). Patients with NHL treated with brentuximab (1.3%) had the highest hazard of peripheral neuropathy (HR=7.00, CI 4.13–11.87), followed by those receiving

vinca alkaloids alone (HR=1.70, CI 1.24–2.31). Paclitaxel, which was used by 22.1% of patients, emerged as the most neurotoxic regimen for patients with breast cancer, both alone (HR=4.03, CI 3.05–5.31) or with carboplatin (HR=3.38, CI 2.18–5.23), followed by docetaxel plus carboplatin (HR=3.24, CI 2.21–4.73). Patients with colorectal cancer who received neurotoxic drugs (63.9%), 98.7% of which was oxaliplatin, had a hazard of peripheral neuropathy 3.5 times higher than those who did not (HR=3.46, CI 2.23–5.36). Patients with testicular cancer who received cisplatin plus etoposide (34.5%) had twice the hazard of peripheral neuropathy compared to those who did not receive these drugs (HR=2.06, CI 1.37–3.11).

Patients with metastatic colorectal cancer were less likely to receive chemotherapy than those with non-metastatic disease (HR=0.6, CI 0.4–0.9) (Supplemental Table S4). Additionally, for colorectal and testicular cancer, risk of peripheral neuropathy was higher among patients who resided in the highest and middle (vs. lowest) socioeconomic neighborhoods, respectively. No associations were found between peripheral neuropathy and other sociodemographic and clinical factors.

Discussion

In a large cohort involving over 6,000 children and AYAs with Medicaid insurance in California diagnosed with five types of cancer, our findings revealed a high 5-year cumulative incidence of peripheral neuropathy ranging from 17% to 70% among the 55% of patients receiving neurotoxic chemotherapy. Across each cancer type, the risk of developing peripheral neuropathy was 1.7 to 9.5 times greater among patients exposed to neurotoxic agents, particularly brentuximab in patients with HL or NHL, paclitaxel in patients with breast cancer, oxaliplatin in patients with colorectal cancer, and cisplatin and etoposide in those with testicular cancer. We identified a substantial risk of peripheral neuropathy in a young population of cancer survivors, despite that this population is thought to be at lower risk than older patients or those with diabetes.^{1,8,23,31}

We observed an increasing cumulative incidence of peripheral neuropathy from years 1 to 2 and continuing through year 5 across all cancer sites, particularly for patients who received neurotoxic drugs. This suggests that new diagnoses may occur later in the survivorship period. However, the increase may also reflect several factors, including delayed coding of a symptom that has been present for a long time, delayed diagnosis of peripheral neuropathy during therapy that progresses over time, or the persistence of lower-grade neuropathy (grade 2) even as more severe neuropathy (grades 3 or 4) resolve. We were unable to determine whether patients continued to receive chemotherapy during the follow-up period (e.g., due to relapsed or refractory disease) or neuropathy resolves over time, which could have influenced the observed increase in cumulative incidence. These findings underscore the importance of monitoring peripheral neuropathy, collecting patient-reported outcomes (PROs) on symptomatology, and adjusting treatment as recommended by clinical practice guidelines.³¹

Our findings align with those reported in prior studies. In patients with HL and NHL, those receiving brentuximab had a markedly high risk of being diagnosed with peripheral

neuropathy.^{24,33} To mitigate the risk, regimens that spare neurotoxic agents – such as replacing brentuximab with nivolumab in patients with newly diagnosed advanced-stage HL – may offer better survival outcomes with fewer adverse effects and lower rates of drug discontinuation.³⁴ Consistent with prior studies, paclitaxel was strongly associated with peripheral neuropathy in breast cancer survivors.^{8,9} Given that paclitaxel dosing is based on body surface area, with high pharmacokinetic variability influenced by patient characteristics, such as age and gender,^{10,35} therapeutic drug monitoring³⁵ and pharmacokinetically-guided dosing may help reduce paclitaxel-associated neuropathy.³⁶

Our study confirmed the significant association between oxaliplatin and peripheral neuropathy in patients with colorectal cancer, as previously reported.^{37–39} A recent study found that factors, such as high body mass index, diabetes, and low physical activity, were associated with increased severity of oxaliplatin-induced peripheral neuropathy, highlighting potential areas for interventions to mitigate the risk and severity of CIPN.¹¹ We observed that AYAs with testicular cancer receiving cisplatin and etoposide had twice the risk of peripheral neuropathy than those receiving non-neurotoxic drugs. This is notable as these drugs are not typically considered to be as neurotoxic as the taxanes or vinca alkaloids. A recent European study showed that long-term survivors of testicular germ cell tumors who received ≥ 400 mg/m² of cisplatin reported poorer physical functioning,⁴⁰ suggesting that more work is needed to identify effective supportive care options for these patients.

The updated 2020 American Society of Clinical Oncology guidelines on Prevention and Management of CIPN reiterated that no agent is proven for the prevention of CIPN. Despite limited data, duloxetine remains the only agent recommended for the management of patients with established painful CIPN, whereas no treatment exists for sensory CIPN.³¹ Therefore, identifying early signs of nerve damage is crucial to guide interventions to prevent long-term or severe neurotoxicity. PRO measures are valid and reliable tools to help physicians and researchers detect clinically significant CIPN.^{41,42} However, the absence of validated PRO measures for neuropathy in pediatric and AYA populations underscores the need for future research to either validate adult scales or develop new instruments for these age groups.¹²

In patients with underlying conditions that increase the risk of peripheral neuropathy, such as diabetes, pre-existing or family history of peripheral neuropathy,³¹ it is important to weigh the risks and benefits of using neurotoxic chemotherapy. Additionally, in patients who experience peripheral neuropathy during treatment, shared decision-making should consider the potential survival benefits when deciding whether or not to continue neurotoxic chemotherapy, particularly in cases of adjuvant treatment administered to patients with lower risk of recurrence, and thus less absolute survival benefit potential.

Our study has several limitations. First, physicians likely underreported peripheral neuropathy in Medicaid claims. This underreporting can result from patients not being asked about or not reporting peripheral neuropathy symptoms, or when physicians do not document this condition, either due to less severe symptoms or the absence of effective treatments.²³ Second, it is possible that some neurotoxic drugs were not fully captured in Medicaid claims, leading to some patients being classified as receiving non-neurotoxic

drugs, which could result in an underestimation of the association we found between neurotoxic agents and peripheral neuropathy. Third, information on cumulative doses and treatment duration is not available in Medicaid claims, preventing us from considering these associations with neuropathy. Fourth, we could not individually evaluate the effect of some drugs (e.g., bortezomib, ixabepilone, trastuzumab emtansine) due to the small number of patients treated with these agents. Finally, our findings among Medicaid enrollees may not be generalizable to individuals with private insurance, other public insurance or those who are uninsured. However, Medicaid enrollees, who accounted for 40% of all children and AYAs with the selected cancers in our CCR cohort, represent a population at higher risk for late-stage diagnosis and treatment-related complications,^{29,43} which makes this group particularly relevant for studying CIPN. Despite the limitations, we consistently demonstrated a high incidence of peripheral neuropathy in survivors treated with neurotoxic chemotherapy, using a large cohort of young patients, recent data, and the innovative linkage between Medicaid claims, CCR, and HCAI. This information is relevant for the next era of symptom prevention and management, for systematic collection of PROs, and for advising patients on what to expect.

In conclusion, our study revealed a substantial burden of peripheral neuropathy in low-income children and AYAs with common malignancies. Across each cancer site, the risk was higher among patients exposed to specific neurotoxic agents, highlighting the need for further for treatment regimens that reduce neurotoxicity and maintain efficacy. Additionally, close monitoring and early diagnosis of peripheral neuropathy are crucial for reducing symptoms and long-term debilitating effects of this common condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

The data that support the findings of this study are available from the California Cancer Registry, the California Department of Health Care Access and Innovation, and Medi-Cal program. Access to these data sources is granted through an application process by the management or data custodians.

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Context Summary

Key Objective

We examined the incidence of peripheral neuropathy and its associations with neurotoxic and non-neurotoxic chemotherapy among children (<15 years) and adolescents and young adults (AYAs, 15–39 years) diagnosed with cancer and covered by Medicaid in California.

Knowledge Generated

Among 6,446 children and AYAs with Hodgkin lymphoma, non-Hodgkin lymphoma, testicular, colorectal, or breast cancer, 55% received neurotoxic chemotherapy. Of those, 16% were diagnosed with peripheral neuropathy during a median follow-up of 4.8 years from diagnosis. Among patients with neuropathy, 71.5% received neurotoxic agents, compared to 28.5% treated with non-neurotoxic therapies. Across all cancer types, neurotoxic agents increased the hazard of neuropathy by 1.7 to 9.5-fold compared to non-neurotoxic chemotherapy.

Relevance

These findings reveal a high incidence of peripheral neuropathy among low-income children and AYAs with common malignancies treated with neurotoxic drugs, highlighting the need to refine treatment guidelines and develop evidence-based interventions to address this debilitating side effect.

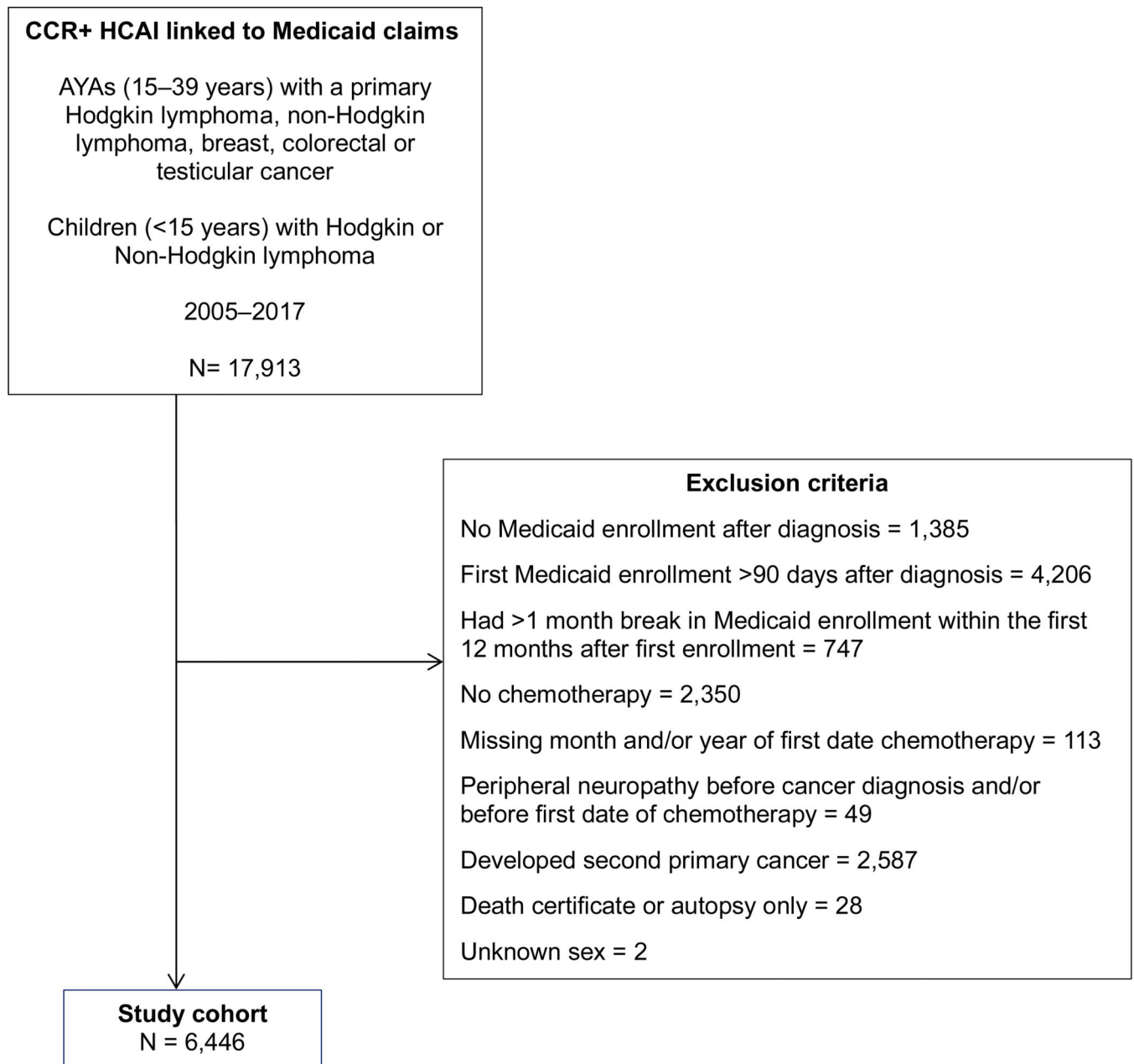


Figure 1:

Study cohort

Abbreviations: AYAs, adolescents and young adults; CCR, California Cancer Registry;
HCAI, Health Care Access and Information

Table 1.
Sociodemographic and Clinical Characteristics of 6,446 Patients Aged 0–39 Years with Medicaid Insurance Diagnosed with Cancer in California, 2005–2017

Characteristics	Total, No. (%)	Absence of peripheral neuropathy No. (Row %)	Presence of peripheral neuropathy No. (Row %)
Age Group at Diagnosis, Years			
Children (0–14) *	418 (6.5)	364 (87.1)	54 (12.9)
AYAs (15–39)	6028 (93.5)	5075 (84.2)	953 (15.8)
Sex			
Male	2571 (39.9)	2202 (85.6)	369 (14.4)
Female	3875 (60.1)	3237 (83.5)	638 (16.5)
Neighborhood Socioeconomic Status			
Lowest	3398 (52.7)	2882 (84.8)	516 (15.2)
Middle	2083 (32.3)	1759 (84.4)	324 (15.6)
Highest	965 (15.0)	798 (82.7)	167 (17.3)
Race/Ethnicity			
Non-Hispanic White	1557 (24.2)	1296 (83.2)	261 (16.8)
Non-Hispanic Black	588 (9.1)	467 (79.4)	121 (20.6)
Hispanic	3659 (56.8)	3134 (85.7)	525 (14.3)
Asian/Pacific Islander	555 (8.6)	471 (84.9)	84 (15.1)
Other/Unknown	87 (1.3)	71 (81.6)	16 (18.4)
Cancer type			
Hodgkin Lymphoma	1173 (18.2)	1012 (86.3)	161 (13.7)
Non-Hodgkin Lymphoma	1157 (17.9)	955 (82.5)	202 (17.5)
Female Breast Cancer	2511 (39.0)	2120 (84.4)	391 (15.6)
Colorectal	704 (10.9)	568 (80.7)	136 (19.3)
Testicular	901 (14.0)	784 (87.0)	117 (13.0)
Stage at Diagnosis			
Non-metastatic (Stages I–III)	4495 (69.7)	3778 (84.0)	717 (16.0)
Metastatic (Stage IV)	1735 (26.9)	1470 (84.7)	265 (15.3)
Unknown	216 (3.4)	191 (88.4)	25 (11.6)
History of Diabetes Mellitus			
Yes	332 (5.2)	255 (76.8)	77 (23.2)
No/unknown	6114 (94.8)	5184 (84.8)	930 (15.2)
Chemotherapy			
Non-Neurotoxic	2885 (44.8)	2598 (90.1)	287 (9.9)
Neurotoxic	3561 (55.2)	2841 (79.8)	720 (20.2)
Taxanes			
Paclitaxel	877 (13.6)	666 (75.9)	211 (24.1)
Docetaxel	694 (10.8)	574 (82.7)	120 (17.3)

Characteristics	Total, No. (%)	Absence of peripheral neuropathy No. (Row %)	Presence of peripheral neuropathy No. (Row %)
Vinca alkaloids			
Vincristine	653 (10.1)	522 (79.9)	131 (20.1)
Vinblastine	536 (8.3)	444 (82.8)	92 (17.2)
Vinorelbine	140 (2.2)	107 (76.4)	33 (23.6)
Platinum			
Oxaliplatin	484 (7.5)	362 (74.8)	122 (25.2)
Carboplatin	636 (9.9)	518 (81.4)	118 (18.6)
Cisplatin	384 (6.0)	315 (82.0)	69 (18.0)
Other neurotoxic drugs			
Eribulin	80 (1.2)	58 (72.5)	22 (27.5)
Etoposide	555 (8.6)	451 (81.3)	104 (18.7)
Ixabepilone	45 (0.7)	41 (91.1)	4 (8.9)
Brentuximab	132 (2.0)	79 (59.8)	53 (40.2)
Trastuzumab Emtansine	47 (0.7)	33 (70.2)	14 (29.8)
Bortezomib	9 (0.1)	7 (77.8)	2 (22.2)

Abbreviations: AYAs, adolescents and young adults.

* Children with non-Hodgkin lymphoma or Hodgkin lymphoma.

Table 2.
Cumulative Incidence of Chemotherapy-Induced Peripheral Neuropathy, by Cancer Type

Chemotherapy	1-year CMI (95% CI)	2-year CMI (95% CI)	5-year CMI (95% CI)
Hodgkin Lymphoma (N=1,173)			
Non-Neurotoxic Drugs	0.96 (0.32–2.32)	1.93 (0.91–3.63)	2.98 (1.63–4.99)
Vinca Alkaloids Only	6.85 (4.87–9.26)	8.67 (6.42–11.32)	12.81 (9.92–16.09)
Brentuximab ^a	8.62 (4.40–14.62)	19.12 (12.51–26.81)	33.22 (24.36–42.33)
Vinca Alkaloid + Etoposide	9.00 (4.40–15.62)	10.00 (5.10–16.84)	13.05 (6.94–21.14)
Other Neurotoxic Drugs	4.17 (0.28–17.99)	4.17 (0.28–17.99)	4.17 (0.28–17.99)
Non-Hodgkin Lymphoma (1,157)			
Non-Neurotoxic Drugs	7.65 (5.85–9.74)	9.53 (7.51–11.82)	11.35 (9.12–13.85)
Vinca Alkaloids Only	14.33 (10.78–18.36)	17.43 (13.53–21.74)	20.25 (16.02–24.84)
Vinca Alkaloids + Etoposide ^b	12.90 (5.98–22.56)	14.52 (7.09–24.48)	18.53 (9.71–29.56)
Brentuximab ^c	25.00 (7.31–47.96)	37.50 (14.62–60.63)	70.31 (37.55–88.10)
Other Neurotoxic Drugs	8.00 (1.33–22.86)	12.24 (2.94–28.61)	12.24 (2.94–28.61)
Breast Cancer (N=2,511)			
Non-neurotoxic Drugs	1.65 (1.00–2.61)	3.13 (2.16–4.38)	5.05 (3.76–6.62)
Paclitaxel ^d	9.83 (7.52–12.50)	14.96 (12.10–18.11)	22.64 (19.02–26.45)
Docetaxel Only	3.63 (1.92–6.18)	5.01 (2.93–7.90)	9.92 (6.62–14.00)
Paclitaxel + Carboplatin ^e	9.35 (5.36–14.69)	13.56 (8.61–19.64)	20.75 (14.21–28.14)
Docetaxel + Carboplatin O	8.43 (5.26–12.53)	13.03 (9.00–17.84)	17.95 (12.91–23.66)
Other Neurotoxic Drugs	5.65 (3.36–8.77)	9.26 (6.23–13.02)	13.84 (10.05–18.23)
Colorectal Cancer (N=704)			
Non-Neurotoxic Drugs	2.45 (1.01–5.00)	4.65 (2.46–7.89)	6.17 (3.52–9.86)
Oxaliplatin/other Neurotoxic ^f	12.83 (9.92–16.13)	19.42 (15.88–23.24)	23.99 (19.99–28.20)
Testicular Cancer (N=901)			
Non-Neurotoxic Drugs	4.70 (3.07–6.83)	5.97 (4.10–8.32)	7.63 (5.45–10.28)
Cisplatin and Etoposide ^g	7.84 (5.17–11.20)	11.92 (8.56–15.87)	16.59 (12.43–21.27)
Other Neurotoxic Drugs ^h	6.95 (2.82–13.64)	9.28 (4.31–16.56)	11.91 (6.06–19.91)

Abbreviation: CMI, Cumulative Incidence; CI, Confidence Interval.

^a Within the 'brentuximab' category, 18 patients with Hodgkin lymphoma received brentuximab only, 96 patients received brentuximab and vinca alkaloids (+/- anything else) and 2 patients received brentuximab with other neurotoxic drug(s) but not vinca alkaloids.

^b Within the 'vinca alkaloid + etoposide' category, among 62 patients who received these drugs, 8 also received other neurotoxic drug (s), except brentuximab.

^c Among 16 patients with non-Hodgkin lymphoma who received brentuximab, 5 also received vinca alkaloids.

^d Within the category 'paclitaxel', 43 patients also received docetaxel at some point during their treatment.

^e Within the category 'paclitaxel + carboplatin', 25 patients also received docetaxel at some point during their treatment.

^f Among the 450 colorectal patients who received neurotoxic drugs, 443 received only oxaliplatin, and only 1 patient did not receive oxaliplatin.

^gIn this category, 275 (88.4%) patients with testicular cancer received cisplatin and etoposide only, and 36 patients received, in addition to these two drugs, any other neurotoxic drug(s).

^hIn the “Other Neurotoxic Drugs”, 21 patients received etoposide without cisplatin and 21 received cisplatin without etoposide.

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Table 3:
Chemotherapy Drugs and Hazard of Developing Peripheral Neuropathy, by Cancer Site

Chemotherapy by cancer site	N (%)	HR (95% CI) ^a	P-value
Hodgkin Lymphoma (n=1,173)			
Non-Neurotoxic Drugs	419 (35.7)	Reference	
Vinca Alkaloids Only	514 (43.8)	3.19 (2.08–4.89)	<.0001
Brentuximab ^b	116 (9.9)	9.53 (5.95–15.26)	<.0001
Vinca Alkaloid + Etoposide	100 (8.5)	4.43 (2.34–8.41)	<.0001
Other Neurotoxic Drugs	24 (2.1)	2.49 (0.85–7.29)	0.0974
Non-Hodgkin Lymphoma (n=1,157)			
Non-Neurotoxic Drugs	724 (62.6)	Reference	
Vinca Alkaloids Only	330 (28.5)	1.70 (1.24–2.31)	0.0008
Vinca Alkaloids + Etoposide ^c	62 (5.4)	1.59 (0.85–2.95)	0.1464
Brentuximab ^d	15 (1.3)	7.00 (4.13–11.87)	<.0001
Other Neurotoxic Drugs	26 (2.2)	1.18 (0.44–3.14)	0.7456
Breast Cancer (n=2,511)			
Non-neurotoxic Drugs	985 (39.2)	Reference	
Paclitaxel ^e	555 (22.1)	4.03 (3.05–5.31)	<0.0001
Docetaxel Only	307 (12.2)	1.91 (1.31–2.77)	<0.0001
Paclitaxel + Carboplatin ^e	150 (6.0)	3.38 (2.18–5.23)	0.0007
Docetaxel + Carboplatin	230 (9.2)	3.24 (2.21–4.73)	<0.0001
Other Neurotoxic Drugs	284 (11.3)	2.70 (1.92–3.79)	<0.0001
Colorectal Cancer (n=704)			
Non-Neurotoxic Drugs	254 (36.1)	Reference	
Neurotoxic Drugs ^f	450 (63.9)	3.46 (2.23–5.36)	<0.0001
Testicular Cancer (n=901)			
Non-Neurotoxic Drugs	503 (55.8)	Reference	
Cisplatin and Etoposide ^g	311 (34.5)	2.06 (1.37–3.11)	0.0005
Other Neurotoxic Drugs ^h	87 (9.7)	1.44 (0.74–2.80)	0.2778

Abbreviation: HR, Hazard Ratio; CI, Confidence Interval.

^a All models were adjusted for age at diagnosis, sex, stage at diagnosis, history of diabetes up to 5 years previous to cancer diagnosis, race/ethnicity, and neighborhood socioeconomic status. Age violated the proportional hazard assumption in the Hodgkin lymphoma and colorectal cancer models and were, therefore, used as stratification variable in the corresponding models.

^b Within the 'brentuximab' category, most patients (n=96) with Hodgkin lymphoma received brentuximab and vinca alkaloids (+/- anything else), 18 patients received brentuximab only, and 2 patients received brentuximab with other neurotoxic drugs (platinum +/-etoposide), but not vinca alkaloids.

^c Within the 'vinca alkaloid + etoposide' category, among 62 patients who received these drugs, 8 also received platinum agents.

^d Among 16 patients with non-Hodgkin lymphoma who received brentuximab, 5 also received vinca alkaloids.

^e Within the category ‘paclitaxel’, 43 patients also received docetaxel at some point during their treatment, whereas within the category ‘paclitaxel + carboplatin’, 25 patients also received docetaxel at some point during their treatment.

^f Among the 450 colorectal patients who received neurotoxic drugs, 443 received only oxaliplatin, 1 received carboplatin and paclitaxel (but not oxaliplatin) and 6 patients received other neurotoxic drugs in addition to oxaliplatin.

^g Within the ‘cisplatin+ etoposide’ category, 275 patients with testicular cancer received cisplatin and etoposide only, and 36 patients received other neurotoxic drugs (taxanes, other platinum and/or vinca alkaloids) in addition to these two drugs.

^h In the “Other Neurotoxic Drugs”, 21 patients received etoposide without cisplatin and 21 received cisplatin without etoposide.