Early Post-Therapy Prescription Drug Usage among Childhood and Adolescent Cancer Survivors

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Objective To describe the patterns of prescription drug use among child and adolescent survivors of cancer in the early post-therapy period compared with matched peers without a cancer history.

Study design Using the MarketScan commercial insurance claims database, we performed a retrospective cohort study identifying survivors of pediatric (0-21 years of age at diagnosis) leukemia, lymphoma, central nervous system, bone, or gonadal cancers who completed therapy from 2000 to 2011 and remained insured for 3 years post-therapy. Prescription fills during the first 3 years post-therapy were examined, categorized by drug class, and compared with age-, sex-, and region-matched individuals without cancer.

Results We identified 1414 survivors and 14 007 comparators. Compared with those without cancer, survivors had 1.5-4.5 times greater risk for filling opioids. Survivors of leukemia, lymphoma, central nervous system, and bone cancers had 2-5 times the risk for antidepressant and 3-7 times the risk for anxiolytic use. Survivors of leukemia, lymphoma, and bone tumors had 3-13 times the risk for angiotensin-converting enzyme inhibitors by the third year post-therapy.

Conclusion Compared with peers without cancer, survivors of childhood cancer have greater rates of prescription use across many drug classes, suggesting greater medical morbidity. Survivors were more likely to use opioid, psychoactive, hormone, and cardiovascular medications. All general pediatricians and subspecialists should be aware of potentially emerging morbidities during the early post-therapy period to guide risk-based surveillance and survivorship care. *(J Pediatr 2017;■■:■■-■■).*

Cancer remains the leading cause of disease-related death in children and adolescents,[1] yet advancements in treatment have led to improved survival. The growing population of childhood cancer survivors in the US will exceed 500 000 individuals by 2020.[2] However, improvements in survival have come with a cost. Because of cancer and its treatment, two-thirds of survivors will develop at least one chronic medical problem within 30 years of diagnosis.[3] Conditions such as cardiovascular disease, endocrinopathies, or psychiatric disorders[2-8] occur more commonly and often arise earlier among survivors, in comparison with the general population, leading to years of disability. It is important that pediatric providers are aware of these risks to provide optimal survivorship care.

Prescription drug use among child and adolescent survivors of cancer can serve as an indicator for morbidity burden. Increased use of psychoactive medications[9-11] and treatments for risk factors of cardiovascular disease (antihypertensive, antihyperlipidemic, and antidiabetic drugs)[12] has been reported. However, these studies focused on patients treated with older regimens,[9,10,12] primarily included patients who were >10 years from diagnosis,[9,10,12] and relied on patient report of medication use.[9,12] Building on these previous studies, we sought to describe prescription drug use in the first 3 years post-therapy among patients with cancer treated with contemporary regimens.

Using a commercial insurance claims database and an algorithm for cancer patient identification combining diagnosis and treatment codes,[13,14] we examined the patterns of prescription fills for all drug classes among survivors of childhood and adolescent leukemia, lymphoma, central nervous system (CNS) tumors, bone cancers, and gonadal cancers—5 of the most common cancer types that span across this age group. We hypothesized that prescription drug usage is greater among survivors of childhood and adolescent cancers compared with age-, sex-, and region-matched children without a history of cancer. We sought to describe the class-specific patterns of use that may reflect chronic morbidities emerging in the early post-therapy period.

ACE	Angiotensin-converting enzyme
CNS	Central nervous system
EOT	End of treatment
RR	Risk ratio

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A.S. is a St Baldrick's Fellow. A.S. and H.N. are supported by the North Carolina Translational and Clinical Sciences Institute (UL1TR001111) and the National Center for Advancing Translational Sciences, National Institutes of Health (KL2TR001109). The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.11.063

Methods

We identified children and adolescents (age ≤21 years at end of treatment [EOT]) treated for leukemia, lymphoma, CNS tumors, bone cancers, or gonadal cancers who completed therapy from January 1, 2000, to December 31, 2011, in the MarketScan Commercial Claims and Encounters Database.[15] This data source includes deidentified inpatient, outpatient, and pharmacy insurance claims data for >50 million individuals and their dependents who are insured by commercial health plans in the US. We identified children and adolescents with the aforementioned cancers using the Agency for Healthcare Research and Quality Clinical Classifications Software[16] matched to *International Classification of Diseases, Ninth Revision*, codes for the diagnoses of interest (**Table I**; available at www.jpeds.com). These 5 cancer types were selected for inclusion as they represent 5 of the most common childhood and adolescent cancers and provide a study sample from across this population's developmental spectrum. Survivors were required to have at least 2 cancer-related visits. We further required that patients have claims for chemotherapy, surgery, or radiation therapy (**Table I**). EOT was defined as 30 days after the last observed treatment date. This included the date of the last inpatient or outpatient claim for chemotherapy or radiation therapy or the date at which an oral chemotherapy prescription would have concluded. We excluded patients with encounter diagnosis codes for 2 or more cancer types or who received a hematopoietic stem cell transplant. Patients were required to have 3 years of continuous health plan enrollment from EOT with no evidence of additional cancer treatment to provide a sufficient period of observation. Because data were available through 2015, subjects must have completed therapy before January 1, 2012, to allow for 3 years of observation.

We selected comparators from children and adolescents in the database without claims for a cancer diagnosis at any time in which they were enrolled in the health plan. Comparators were individually matched for 3-year continuous enrollment profile as determined by the matched survivor's EOT year, age, sex, and geographic region. Separate comparator cohorts were created for each cancer type. Comparators were randomly sampled at approximately a 10:1 ratio. The study design was reviewed by the University of North Carolina School of Medicine institutional review board and classified as not human subjects research.

Measures

The primary study outcomes were (1) any prescription fill, by cancer type and year post-therapy, and (2) drug class–specific use. Drug classes were defined via the Red Book classifications.[17] The proportions of survivors and comparators with at least 1 fill per year post-therapy were determined. The number of fills of unique drug classes per person, and the specific classes of these fills also were determined. Prescription fills among survivors were then categorized by therapeutic groups. Class-specific fills from the most commonly prescribed therapeutic groups among survivors (anti-infectives, CNS, hormonal, gastrointestinal, pulmonary, and cardiovascular agents) were compared with those among individuals without cancer.

Statistical Analyses

We compared the median number of prescriptions and unique drug classes filled by year between survivors and matched comparators using Wilcoxon rank-sum tests. The risk of class-specific prescription drug use by year for survivors and matched controls was estimated with unadjusted risk ratios (RRs) and 95% CIs. As a sensitivity analysis, RRs and 95% CIs were determined with a Poisson regression model adjusted for age, sex, region, and year to account for residual confounding after matching. Minimal differences were noted between the unadjusted and adjusted RRs, so the unadjusted estimates are presented. Statistical analyses were performed with SAS Version 9.4 (SAS Analytics, Cary, North Carolina).

Results

Study Sample

We identified 1414 survivors of childhood cancers and 14 007 matched comparators (**Figure 1**; available at www.jpeds.com). Survivors of gonadal cancers (mean age 17.4 years [SD 3.4]) and lymphoma (15.6 years [SD 4.2]) were older than survivors of CNS tumors (10.1 years [SD 5.3]) and leukemia (9.3 years [SD 5.2]). There was a slight male predominance in the study sample (58%), with the highest sex differential among survivors of gonadal tumors (75% male). More patients were from the South and more were treated from 2009 to 2011, reflective of enrollment patterns for health plans included in the MarketScan database (**Table II**).

Quantifying Prescription Fills among Survivors and Comparators

More survivors than comparators filled prescriptions. Across cancer types, 84%-91% of survivors filled at least 1 prescription in the first year off therapy, and this declined to 70%-81% by the third year post-therapy. Approximately 60% of comparators filled at least 1 prescription per year. Throughout the study period, survivors were at 20%-50% greater risk than comparators for having filled a prescription. This increase in prescription fills was present for survivors of all cancer types and across all 3 years of observation (**Figure 2**).

In addition, survivors were more likely than comparators to fill prescriptions from multiple drug classes. Although survivors filled prescriptions from 4-8 drug classes per person in year 1, and 2-6 classes in years 2 and 3, comparators typically filled drugs in 1 class per year (**Table III**). Survivors of CNS tumors filled prescriptions from the most drug classes (6-8 classes/person-year), and survivors of gonadal tumors filled prescriptions from the fewest number of classes (2-4 classes/person-year).

Nearly one third of all prescriptions filled by survivors were for anti-infectives (antibacterials, antifungals, antivirals). Compared with individuals without a history of cancer, survivors of all cancer types were at increased risk for filling antibacterial prescriptions in all 3 years of the study period (**Figure 3**,

FLA 5.5.0 DTD ■ YMPD9636_proof ■ January 30, 2018