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Vincristine Associated Neuropathy with Antifungal Usage: A Kaiser Northern California Experience

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Abstract

The dose limiting toxicity for vincristine is peripheral neuropathy which can be potentiated with concurrent usage of azole antifungals. The current retrospective study assessed the incidence of concurrent vincristine and azole antifungal usage to determine if it led to increased neurotoxicity for the Kaiser Northern California pediatric acute lymphoblastic leukemia (ALL) and Hodgkin lymphoma patient population. Data was obtained from the electronic medical record (2007–2014). 130 subjects received a least one dose of vincristine for ALL or Hodgkin lymphoma (median age 9, 88% ALL, 58% male, 47% Caucasian). 31% of patients received concurrent antifungal usage (fluconazole 78%, voriconazole 10%, fluconazole/voriconazole 12%), however concurrent antifungal usage accounted for less than 15% of vincristine doses. Grade 2 or greater neuropathy occurred in 51% of patients; Grade 3 neuropathy was present in 8% of patients. No difference in the incidence of grade 2 or greater neuropathy was observed with the concurrent use of antifungal therapy ($p=0.35$), gender ($p=0.59$), type of cancer ($p=0.41$), ethnicity ($p=0.29$), or age ($p=0.39$), but was higher with increasing amount of vincristine doses ($p=0.004$). These results suggest that concurrent azole antifungal usage with vincristine for patients with ALL and Hodgkin lymphoma was low in the Kaiser Northern California population and limited usage as needed may be reasonable and safe.

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Conflicts of Interest:

Dr. Capparelli serves on the data safety and monitoring board for Cempra Pharmaceuticals and The Medicines Company and has received consulting fees from Aptose, Plexxikon, Atox Bio Ltd, Celltrion, and Patara.

Keywords

vincristine; neuropathy; azole antifungal; ALL; Hodgkin lymphoma

INTRODUCTION

Vincristine is an antineoplastic agent used for treatment of many cancers including acute lymphoblastic leukemia (ALL) and Hodgkin lymphoma. It prevents chromosome separation in metaphase by binding to tubulin, ultimately leading to cell death. The dose-limiting toxicity is peripheral neuropathy¹ with metabolism occurring predominantly through CYP3A4 and CYP3A5². Leukemia and lymphoma patients are at risk for fungal infections and many are treated with azole antifungals while receiving doses of vincristine. Despite the increased risk of infection, there is currently insufficient evidence to make guidelines regarding prophylaxis for pediatric patients with ALL or Hodgkin lymphoma; however certain populations may be at higher risk for fungal infections and receive prophylactic azole antifungals concurrently with vincristine^{3,4}. The azole antifungals have the potential to increase drug levels through CYP3A4 inhibition and inhibition of P-glycoprotein mediated vincristine efflux⁵, thus there is concern for increased toxicity with concurrent usage. Prior studies have indicated that there is increased vincristine toxicity with prophylactic antifungal usage^{6,7} while others have not found this effect⁸. It is still unclear how often concurrent usage occurs and whether limited duration concurrent usage would lead to increased toxicity.

The Kaiser Permanente Northern California health care system represents 4 million patients with an electronic medical record dating back to 2007. Patients with Kaiser Foundation health insurance receive all of their medical care in a single system of hospitals, clinics, and pharmacies. A comprehensive description of antifungal and vincristine usage over the course of therapy can thus be obtained from review of these medical records.

The current retrospective study aimed to determine the incidence of concurrent vincristine and azole antifungal use and if this drug combination led to increased neurotoxicity in ALL and Hodgkin lymphoma for the Kaiser Northern California pediatric patient population. It assessed the effects of demographics and cumulative vincristine exposure on neurotoxicity.

MATERIALS AND METHODS**Patient population and data extraction**

The retrospective cohort comprised patients less than 22 years of age who were treated in the Kaiser Permanente Northern California medical system. Patients were identified as those who had received vincristine and had a diagnosis of ALL or Hodgkin lymphoma from the start of the electronic medical record system (January 2007) to the date of the data pull (February 2016). Dates of all vincristine inpatient and outpatient drug administrations were extracted electronically. All azole antifungal (fluconazole, voriconazole, posaconazole, and itraconazole) inpatient drug administrations and outpatient prescriptions were pulled electronically. Demographic information including age, ethnicity (self-reported), and gender

were also electronically extracted. Drug administrations of commonly used strong CYP3A4 inhibitors (ritonavir) and inducers (carbamazepine, phenytoin, phenobarbital, oxycarbazepine) were also electronically extracted. Neuropathy information was determined through chart review of oncology notes.

Data analysis

Concurrent antifungal usage—Patients were identified who had received concurrent vincristine and antifungal usage. To ensure that patients were receiving vincristine and azole antifungal concurrently, a minimum degree of overlap between administrations was defined (Figure 1). Given the median half-life of 85 hrs (range: 19–155 hrs) for vincristine⁹, patients who received a dose of antifungal within 7 days after the vincristine dose were considered to have concurrent usage. Patients had to receive fluconazole, posaconazole, or itraconazole four or fewer days prior to administration of vincristine given the approximately 30 hr half-life of the drugs^{10–12}. For voriconazole, the vincristine usage had to be within 1 day, given the reported 6 hr half-life of the drug¹³. Patients with overlap of antifungal and vincristine dosage at least once during treatment were considered to have concurrent usage. Those with outpatient antifungal prescriptions were assumed to be taking the antifungal for the total amount of days that the drug was prescribed.

Identification of Neuropathy—All oncology notes from the start of vincristine administration to thirty days after the final administration were reviewed to assess for the presence of neuropathy. Neuropathy was scored using the ECOG scale (Table 1)¹⁴. If multiple mentions of neuropathy occurred, then the highest grade was used for the analysis. Patients with pre-existing neuropathy were excluded from the analysis.

Statistics—Fischer's exact tests were used to compare the presence or absence of grade 2 or greater neuropathy to categorical variables (antifungal use, ethnicity, gender, disease) to the incidence of grade 2 or greater neuropathy. The Wilcoxin rank sum test was used to compare the presence of grade 2 or greater neuropathy to continuous variables (age, vincristine doses).

RESULTS

In total, 130 patients receiving vincristine for ALL or Hodgkin lymphoma were identified from the electronic medical record. An additional 8 patients receiving vincristine had pre-existing neuropathy and were excluded from the analysis. The median age was 9 years (range: <1–21 years). 75 (58%) patients were male and 55 (42%) were female. 47% were Caucasian with 4% African American, 18.5% Asian, 28.5% Hispanic, and 2% American Indian. The majority of patients were treated for ALL (88%). There were a total of 3,475 vincristine doses administered with a median of 24 per patient (range: 1 to 72). 41 patients (31%) received concurrent antifungal usage (fluconazole 32, voriconazole 4, and fluconazole/voriconazole 5) (Figure 2A). Median number of times of antifungal overlap per patient was 2 (range: 1–14) and occurred in 12% of vincristine doses. Only one patient in the study received a CYP3A4 inducer (phenytoin) concurrently with vincristine administration.

This patient was included in the analysis since the grade 2 neuropathy developed after 14 vincristine doses, but prior to concurrent phenytoin usage.

Neuropathy (grade 2 or higher) was documented in 66 patients (51%) with 10 patients (8%) having grade 3 neuropathy. The majority of documented neuropathy involved the absence deep tendon reflexes (~75%) without additional information regarding other motor or sensory neuropathy. After initial documentation of neuropathy, it was confirmed in a second note in 74% of subjects, and in at least two additional notes in 42% of subjects. Given the low incidence of grade 3 or greater neuropathy, statistical comparisons were limited to grade 2 or greater neuropathy (Table 2). No difference in the incidence of grade 2 or greater neuropathy was observed with the concurrent use of antifungal therapy (Figure 2B, $p=0.35$). No difference in the incidence of grade 2 or greater neuropathy was observed with the concurrent use of voriconazole vs. fluconazole or no azole usage ($p=0.49$). The time to develop grade 2 neuropathy was also not different with the use of antifungal (Figure 3). Grade 3 neuropathy developed later than grade 2. No differences in the presence of grade two or greater neuropathy were observed for gender ($p=0.59$), disease status (ALL vs. Hodgkin lymphoma; $p=0.41$), ethnicity ($p=0.29$), African-American vs. other ethnicities ($p=0.37$), or age ($p=0.39$). The number of vincristine doses was strongly related to the incidence of grade 2 or greater neuropathy (Figure 4, $p=0.004$). The amount of antifungal overlap per patient was derived from outpatient azole prescriptions in 25 out of the 41 patients in the antifungal group. Since 85% of patients received at least one course of inpatient with or without outpatient antifungal, we believe that the comparison between the presence of any concurrent antifungal usage and neuropathy is valid, however the data was not felt to be granular enough to compare the total amount of overlap to the occurrence of neuropathy.

There were 10 patients with grade 3 neuropathy and 6 of the 10 experienced severe weakness. Five of the 10 patients had concurrent antifungal usage. Total vincristine doses ranged from 14 to 49 (median: 27) in patients without antifungal overlap and from 14 to 32 (median: 22) in patients with antifungal overlap. There were 5 African American patients in the study and 4 of these patients had grade 2 neuropathy. No grade 3 neuropathy was seen. Three of the five patients received concurrent antifungal.

DISCUSSION

Leukemia and lymphoma patients can develop invasive fungal infections over the course of treatment which may require azole antifungal administration. Vincristine is a commonly used drug in leukemia and lymphoma regimens. Vincristine induced peripheral neuropathy involves both sensory and motor functions. The mechanism of action of vincristine is binding to beta-tubulin which prevents cell division and leads to cell death. The disruption of the beta-tubulin assembly and disassembly leads to swelling and ultimately damage of myelinated and unmyelinated nerve fibers^{1, 15}. Thus the incidence and severity of symptoms would be expected to be related to the duration and dose received by patients. Since azole antifungals are CYP3A4 inhibitors and vincristine is a CYP3A4 substrate, concurrent antifungal usage places patients at risk of worsening dosing limiting peripheral neuropathy and compromising the administration of full dose curative therapies. The current

study aimed to characterize concurrent antifungal usage patterns in patients with ALL and Hodgkin lymphoma patients and determine if it increased the incidence of higher grade (2 or greater) peripheral neuropathy.

Overall concurrent antifungal usage accounted for 12% of the total vincristine doses in a patients, thus the frequency of concurrent usage was small. No differences were seen between incidence of grade 2 or greater neuropathy and antifungal usage. No differences in grade 2 or greater neuropathy were present based on age, ethnicity, disease status, or gender. The number of vincristine doses was higher in patients with neuropathy.

There were more patients with concurrent antifungal usage in the grade 3 neuropathy group (50% as compared to 30%). However due to the low incidence of reported grade 3 neuropathy the study was underpowered to find a difference. African-American patients were few in the study and did not have grade 3 neuropathy. Prior studies suggested that that the higher expression of CYP3A5 allows these patients to metabolize the drug better leading to decreased toxicity albeit with decreased efficacy due to lower vincristine drug levels ¹⁶.

Although the current study was retrospective, Kaiser Northern California is a closed system with patients receiving all of their care, chemotherapy, and prescriptions within the same network of hospitals, thus the information in the electronic medical record represents a complete medication record. However determining concurrent usage of antifungal and vincristine administration was still challenging for patients receiving outpatient antifungals as this was based on prescriptions. Information regarding whether the patient filled the prescription, if the medication was started, and if the medication was held was lacking in the electronic data extraction and chart review. Since 85% of patients had at least one course of inpatient with or without outpatient antifungal, we believe that the comparison between concurrent antifungal usage and neuropathy is valid. However we do not have the granularity in the data to compare amount of concurrent usage to the occurrence of neuropathy.

There have been several studies looking at vincristine associated toxicity with concurrent antifungal usage. Moriyama et al investigated at the incidence of adverse drug reactions with vincristine and azole antifungals through literature review and found the most common adverse drug reactions in pediatrics were: gastrointestinal (86%), electrolyte abnormalities (62%), autonomic neuropathy (62%), and peripheral neuropathy (48%) ¹⁷. Van Schie et al studied at 20 pediatric ALL patients to compare the incidence of vincristine toxicity in the presence and absence of azole antifungal prophylaxis and found that constipation and peripheral neuropathy were significantly increased ⁶. The majority of patients received itraconazole prophylaxis which may provide increased toxicity due to potential inhibition of P-glycoprotein in addition to CYP3A4, as compared to the current study where patients received fluconazole or voriconazole. Teusink et al found that fluconazole prophylaxis during induction chemotherapy for pediatric ALL resulted in a significant increase in the incidence of neuropathy, but no differences in GI toxicity ⁷. In contrast, Smitherman et al studied fluconazole prophylaxis during induction therapy for pediatric ALL and did not find an increased risk of vincristine related toxicity. There was an increased risk of vincristine toxicity in patients 10 years and older which was independent of fluconazole usage ⁸.

Between study comparisons of neuropathy is complicated by variability in scoring systems. The current study used the ECOG scoring system, finding a 51% rate of grade 2 or greater neuropathy and 8% rate of grade 3 or higher neuropathy. This is higher than that observed in a prior prospective study of pediatric ALL which found 27% grade 2–4 neuropathy with 11% grade 3 or greater neuropathy using the CTCAE scoring system¹⁸. A separate prospective pediatric ALL study using the TNS scoring system found 78% of children had vincristine induced peripheral neuropathy of any grade and in these patients CTCAE-derived grades 1, 2, 3, and 4 sensory neuropathy occurred in 31%, 3%, 2%, and 0%, and motor neuropathy in 18%, 4%, 2%, and 0% of children, respectively¹⁹. As the current study was retrospective and the majority (~75%) of the documented neuropathy was related to the presence of absence of deep tendon reflexes without other details on sensory or motor neuropathy, the authors used the ECOG scoring system to best capture the neuropathy information available in the electronic medical record. A prior study found higher rates of chemotherapy induced peripheral neuropathy with prospective evaluations as compared to a retrospective evaluation of the electronic medical record²⁰. Although we found higher rates of neuropathy than other prior prospective pediatric studies, this remains limitation of the current retrospective study. Prospective collection of data would likely have yielded higher rates of neuropathy and more granularity on the types of neuropathy.

Patients who received anti-fungal administration within 7 days of the vincristine dose were considered to have concurrent usage in order to capture all possible concomitant usage. However, the majority of vincristine may be metabolized within the first 24 hours. Using a more stringent cut-off of one day for antifungal administration after vincristine dose and the same criteria for anti-fungal usage prior to vincristine dose resulted in 6 fewer patients with concurrent antifungal usage, but still did not yield a significant difference in the incidence of grade 2 or greater neuropathy with the concurrent use of antifungal therapy ($p=0.32$). Patients with concurrent usage received almost exclusively fluconazole (78%) which is considered a weaker CYP450 inhibitor than voriconazole, posaconazole, or itraconazole, thus a difference in the frequency of neuropathy may have been found in a patient population receiving more potent antifungals. While the mg/m^2 vincristine per dose may also relate to toxicity, this information was incompletely extracted from the database thus could not be evaluated in the current study.

The study cannot make conclusions about prolonged usage of azole antifungal as prophylaxis or treatment in the setting of multiple vincristine doses. However, overall the current results suggest that concurrent azole antifungal usage with vincristine for pediatric patients with ALL and Hodgkin lymphoma patients was low in the Kaiser Northern California population and this limited usage as needed may be reasonable and safe.

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Figure 1.

Concurrent antifungal usage. A. Patients with antifungal administered during or within 7 days after vincristine usage were considered to have concurrent vincristine and antifungal usage. B. Vincristine administered within 4 days of fluconazole, posaconazole, or itraconazole or within 1 day of voriconazole was considered concurrent vincristine and antifungal usage.

Figure 2.

A. Concurrent antifungal usage and types of antifungal used. 31% of patients received concurrent antifungal: fluconazole (25%), voriconazole (3%), or both fluconazole and voriconazole (3%). B. Percentage of patients with grade 2 or greater neurotoxicity with and without concurrent antifungal usage. There was no difference in the incidence of neurotoxicity with the use of antifungal ($p=0.35$). Error bars represent 95% confidence intervals of the proportion.

Figure 3.
Time to first neuropathy. No differences were seen between in the time to develop neuropathy with or without the use of antifungal for grade 2 neuropathy. Grade 3 neuropathy developed later than grade 2.

Figure 4. Vincristine doses vs. incidence of grade 2 or greater neurotoxicity. The incidence of neurotoxicity was strongly related to total number of vincristine doses ($p=0.004$).

Table 1

ECOG neuropathy scale: grades and symptoms

0	1	2	3	4
None	Decreased DTR Mild paresthesias Mild constipation	Absent DTR Severe paresthesias Severe constipation Mild weakness	Disabling sensory loss Severe neuropathic pain Severe weakness Bladder dysfunction Constipation	Respiratory dysfunction secondary to weakness Constipation requiring surgery Paralysis (chair or bedbound)

Table 2

Presence neuropathy with demographics, antifungal usage, and vincristine dose

	No Neuropathy	Neuropathy	p-value
Grade 2 or greater neuropathy			
N (%)			
Concurrent antifungal	23 (36%)	18 (27%)	0.35
Ethnicity (White)	30 (47%)	31 (47%)	0.29
African-American	1 (2%)	4 (6%)	0.37
Disease (ALL)	51 (85%)	59 (91%)	0.41
Gender (Male)	35 (55%)	40 (61%)	0.59
Median (IQR 25% – 75%)			
Age (years)	11 (3 – 16)	8 (4 – 15)	0.39
Number of Vincristine Doses	17 (8 – 38)	27 (14 – 49)	0.004
Grade 3 or greater neuropathy			
N (%)			
Concurrent antifungal	36 (30%)	5 (50%)	0.29
Ethnicity (White)	56 (47%)	5 (50%)	1.00
African-American	5 (4%)	0 (0%)	1.00
Disease (ALL)	100 (87%)	10 (100%)	0.61
Gender (Male)	69 (58%)	6 (60%)	1.00
Median (IQR 25% – 75%)			
Age (years)	9 (4 – 15)	7 (4 – 17)	0.37
Number of Vincristine Doses	24 (9 – 24)	26 (18 – 31)	0.13