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Pediatric Acute Lymphoblastic Leukemia Patients and Potential Risk for Vincristine Side Effects with Concomitant Fluconazole

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Introduction

- Pediatric Acute Lymphoblastic Leukemia (ALL) treatment involves the administration of vincristine (VCR), an anticancer drug that inhibits cell replication during mitosis.^[1]
- There are various side effects of vincristine therapy, including neuropathy (sensory, motor, autonomic), electrolyte abnormalities (namely, hyponatremia from SIADH), and GI symptoms.
- Patients undergoing ALL treatment are at high risk for opportunistic infections, including invasive fungal infection (IFI).^[2]
- To prevent IFIs, some patients receive antifungal prophylaxis. Our institution primarily prescribes fluconazole.^[3]
- Fluconazole inhibits metabolism of vincristine by acting as a substrate and inhibitor of CYP3A4.^[6-8] Because of their inhibition of vincristine metabolism, azoles can potentiate some of the side effects of vincristine.^[4,5,6]
- We analyzed whether the use of fluconazole prophylaxis impacts vincristine's side effects during induction therapy.

Method

- We conducted a retrospective chart review of all pediatric (age 0-18 years) patients diagnosed with ALL at Children's Hospital and Medical Center in Omaha, Nebraska from July 2013-May 2021.
- We collected data on demographics, disease characteristics, and treatment protocol.
- Patients were divided into two groups based on whether or not they received fluconazole.
- Incidence of fungal infection, rate and grade of peripheral neuropathy, and prescription for gabapentin (treatment for peripheral neuropathy) were collected for both groups.
- Sodium nadir during induction was noted for both groups, as an indication for development of SIADH.
- Statistical analysis was performed by applying an ordinal logistic regression.

Results

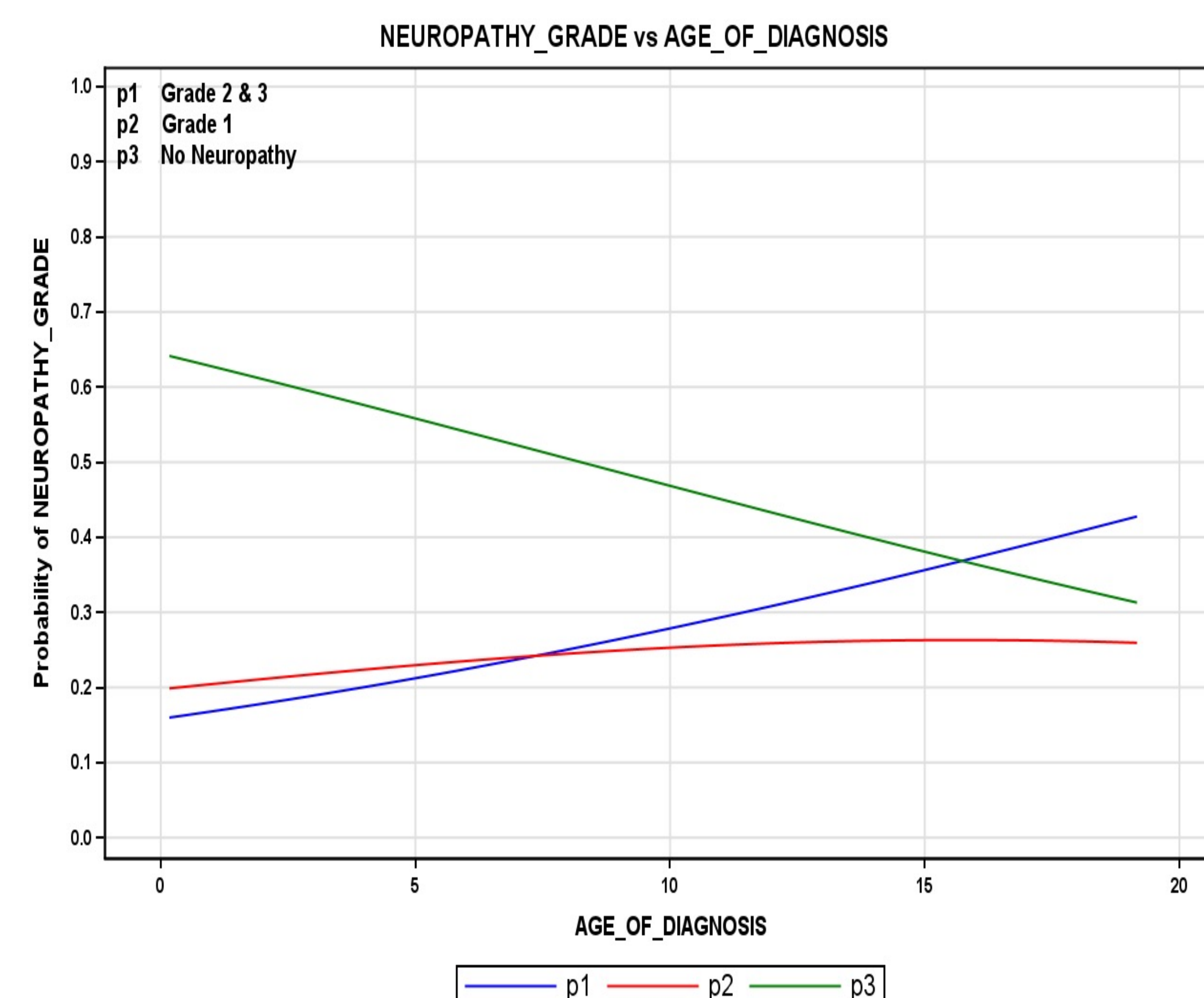
Table 1. Patient's Characteristics by Fluconazole Exposure

Patient's Demographics	Number of Patients (n=157)
Age of Diagnosis (years)	
Mean	7.13
Median	5.43
Gender	
Male	74 (47.13%)
Female	83 (52.87%)
Race	
White	112 (71.34%)
Hispanic	27 (17.19%)
Two or More Races	11 (7.01%)
African American	3 (1.91%)
African	2 (1.27%)
Asian	1 (0.64%)
Other	1 (0.64%)
Ethnicity	
Hispanic	36 (22.93%)
Non-Hispanic	121 (77.07%)
Fluconazole	
Yes	72
No	85

Table 2. Sodium Levels and Peripheral Neuropathy According to Fluconazole Exposure

Variables	Fluconazole	No Fluconazole	P value
Sodium Levels			<0.001
>135	53 (73.61)	15 (17.65)	
131-134	8 (11.11)	31 (36.47)	
121-130	11 (15.28)	39 (45.88)	
Peripheral Neuropathy			0.28
Grade 0	42 (58.33)	39 (45.88)	
Grade 1	14 (19.44)	23 (27.06)	
Grade 2 & 3	16 (22.22)	23 (27.06)	

Table 3. Comparison of Neuropathy Grade with the Age of Diagnostic



Discussion

- Our data did not find a correlation between fluconazole use and increased incidence of peripheral neuropathy (p value = 0.28)
- Interestingly, fluconazole use did not increase the rate of hyponatremia but is associated with less hyponatremia (p value = <0.001)
- Lack of fluconazole prophylaxis did not increase the rate of fungal infection in this study. In fact, the two cases of reported fungal infections were noted in patients receiving fluconazole prophylaxis.
- Patients' ethnicity did not influence occurrence of neuropathy (OR 1.33, p = 0.43) or hyponatremia (OR = 0.0584, p = 0.14)
- As the age at diagnosis increased, the presence of hyponatremia increased compared to normal. Incidence of higher-grade neuropathy also increased as the age at diagnosis increased.

Conclusion and Future Directions

- We did not find a statistically significant difference that the use of concomitant fluconazole with vincristine increased the risk of peripheral neuropathy or hyponatremia.
- Our results help to clarify that the concomitant use of fluconazole with vincristine for ALL treatment is safe and does not increase the risk of side effects
- Further investigation needs to be done to explore the association between age at diagnosis and increased hyponatremia and neuropathy using multivariate analysis.

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