Supplement-1

"Chemotherapy regimen and drug interactions."

To determine the role of voriconazole (VCZ) in inducing PRES, we assessed all the consumed drugs' bio-pharmacy equations, half-life and washout period**s** with considering relevant drug interactions to rule out the role of other possible drugs that could've induced latter phenomena.

Case 1
A 5-year-old boy from Iranian descent with confirmed Acute lymphoblastic Leukemia (ALL).
Patient's BSA: 0.766, BW: 17 kg, height: 119 cm. (BUN: 10 to 22 and Creatinine: 0.1 to 0.4 with normal GFR)

Induction chemotherapy:
Dexamethasone (6 mg/m^2 on day 1-28, half-life in children 4 months to 16 years: 4.34 ± 4.14 hours (range: 2.33 to 9.54 hours) [Up-to-date], maximum washout period: 20 hours**)**, **Vincristine** (1.5 mg/m^2 on day 1, 8, 15, and 22, half-life elimination (terminal): 85 hours (range: 19 to 155 hours) [Up-to-date], maximum washout period: 15 days), **Adriamycin** (30 mg/m^2, half-life: 54 hours; [Up-to-date], maximum washout period: 11 days), **Methotrexate** (4 gram/m^2, half-life: 0.7 to 5.8 hours (dose range: 6.3 to 30 mg/m2); [Up-to-date], maximum washout period: 29 hours). **Cytarabine** (Intrathecal 40 mg on day 1), cytarabine in the cerebrospinal fluid declined with a first order half-life of about 2-hours. [dailymed.nlm.nih.gov FDA], maximum washout period: 10 hours).
Methotrexate (Intrathecal 12 mg on days 8 and 29), the mean antifolate value in the lumbar CSF declined in a biphasic manner with half-lives of 4.5 and 14 hours. In the plasma, the mean MTX concentration reached a peak of 2 X $10^{(-7)}$/Mole between 3 and 12 hours after injection and decreased biexponentially after that with half-lives of 5.5 and 24 hours. [Bleyer WA, Dedrick RL. Clinical pharmacology of intrathecal methotrexate. I. Pharmacokinetics in nontoxic patients after lumbar injection. Cancer Treat Rep. 1977;61: 703-8], maximum washout period: 3 days.)

Intensification phase:
Prednisolone 120 mg/m^2 (first 5 days in each 21 days course, half-life elimination: 2 to 4 hours; [Pickup 1979], [Up-to-date], maximum washout period: 20 hours), Oral 6-mercaptopurine (50 mg/m^2 on day 1 to 14 in each 21 days course), **Oral 6-mercaptopurine** (50 mg/m2 on day 1 to 14 in each 21 days course, half-life

elimination (Tablets): Children: 21 minutes. [Up-to-date], maximum washout period: 4.3 hours). **Vincristine** 1.5 mg/m^2 (each 21 days course), **Adriamycin** 30 mg/m^2 (each 21 days course), **L-asparaginase** 25000 IU/m^2 (weekly for 20 weeks, half-life elimination: ~16 hours (following a single IM dose). [Douer, 2007], [Up-to-date], maximum washout period: 3.3 days.), and intrathecal (IT) **Cytarabine** (40 mg), **Methotrexate** (12 mg), and **Hydrocortisone** (12 mg) every 8 weeks.

Accordingly, he was on dexamethasone and vincristine at the time of VCZ administration, which was concordant with the 25th day of chemotherapy. He developed first signs and symptoms of PRES on the 15th day of the intensification phase (43th day of chemotherapy), while he was on the daily 6-mercaptopurine and weekly L-asparaginase. He received 4 ITs chemotherapy courses (one cytarabine, two MTX, and one triple), and the closest IT was more than two weeks before the first-time seizure.

MTX, vincristine, and prednisolone are known to play a role in the development of PRES in T-cell ALL patients, especially during the first four months of chemotherapy (1). The patient also received pantoprazole in addition to supplements during his admission.

We evaluated the neurotoxicity of all the drugs as mentioned above to determine the pertinent drugs in inducing PRES. By assessing the pharmacological aspect and half-life of the established drugs, none of the anti-cancer agents could have interfered with PRES, except for vincristine (known to cause peripheral neuropathy) and 6-mercaptopurine (with no significant recorded role in neurotoxicity). While MTX could be the most probable agent that could have induced encephalopathy, but with the calculated half-life and washout period, MTX serum and CSF concentrations were at least levels at the time of PRES; makes it unlikely to be the responsible drug in inducing PRES in case 1. Except for VCZ, MTX and other drugs continued based on his protocol. Although leukemic patients are prone to develop PRES even 20 weeks after chemotherapy, it usually develops in the 3rd and 4th weeks following chemotherapy (1). Our case, however, developed PRES symptoms 6th weeks after the onset of chemo, so VCZ certainly played a more prominent role in inducing PRES than the underlying disease. Altogether, while the PRES might develop secondary to chemotherapy in leukemic patients, we should not disregard other possible associated factors. When this severe complication attributed to anti-cancer drugs, there may be essential challenges such as dose reduction, protocol change, or delaying treatment, resulting in an increased risk of relapse (1). On the other hand, VCZ, which frequently used in the oncology setting, could also induce PRES. The probability

of unanticipated case reports in an insignificant number of individuals could be validated by quantitative safety signal techniques (2). Re-analyzing this theory based on recent WHO and FDA database by Rob van Manen, emphasized on the high potential of VCZ-induced PRES (supplement-2).

Interactions

A. Patient's medications and drug-drug interactions based on Lexi-Interact (Lexicomp®, Wolters Kluwer, last update 27 December 2019) prior and by the time of PRES development, *day 30-45*:

During this period, he had normal renal function (BUN: 10 to 22 and Creatinine: 0.1 to 0.4 with normal GFR) but abnormal liver function tests (Child-Turcotte-Pugh class score C).

[SMX/TMP and MTX]; [linezolid and granisetron]; [mercaptopurine and SMX/TMP]; [pantoprazole and MTX]; [SMX/TMP and linezolid] and [pantoprazole and pantoprazole]:

None of the possible interactions could explain neurotoxicity and induced PRES. However, L-asparaginase was discontinued, based on oncologist opinion and abnormal liver function tests.

B. Patient's medications and drug-drug interactions based on Lexi-Interact (Lexicomp®, Wolters Kluwer, last update 27 December 2019), *day 10-25* (the onset of VCZ consumption):

During this period, he had normal renal function (BUN: 5 to 15 and Creatinine: 0.5 to 0.8 with normal GFR) and also normal liver function tests.

[piperacillin-tazobactam and vancomycin]; [VCZ and Vincristine]; [VCZ and pantoprazole]; [pantoprazole and MTX]; [piperacillin-tazobactam and MTX]; [piperacillin-tazobactam and amikacin]; [amikacin and amphotericin]; [amikacin and vancomycin]; [Vincristine and amphotericin]; [levothyroxine and pantoprazole]; [Vincristine and amphotericin]; [VCZ and amphotericin]; [dexamethasone and VCZ]; [granisetron and VCZ]; and [dexamethasone and amphotericin], [caspofungin and dexamethasone]:

None of those, as mentioned earlier, drug-drug interactions could explain high-VCZ trough levels. Other considerations:

1. VCZ might have increased risk of vincristine associated peripheral neurotoxicity.
2. PPIs could have increased the serum concentration of MTX.
3. Piperacillin-tazobactam might have increased the serum concentration of MTX.

4. Proton Pump Inhibitors (PPIs) might have increased VCZ serum concentration. PPIs dose reduction is recommended when 40 mg/day or a greater dose of omeprazole or 60 mg/day of lansoprazole were administrated. Such a report has not stated for pantoprazole and ilaprazole (Lexi-Interact (Lexicomp®, Wolters Kluwer, last update 27 December 2019).

On the 25th day of chemotherapy, only vincristine and dexamethasone still had therapeutic levels in plasma. Accordingly, based on the possible drug interactions between VCZ, vincristine, and dexamethasone, only VCZ and vincristine constitute a significant concern. VCZ is a CYP3A4 potent Inhibitor and might decrease the metabolism of CYP3A4 substrates (vincristine) that could have amplified vincristine's side effects such as peripheral neuropathy. There is no report of increased risk of any type of encephalopathy during concurrent VCZ, and vincristine coadministration.

Case 2

Twelve years old girl from Iranian descent, suffering from Wilms tumor. Patient's BSA: 1.015 m^2, BW: 25.5 kg, height: 140 cm, BUN: 11-17, Creatinine: 1.08-1.3, and GFR: 75.38-90.74 mg/dl. Liver function tests: ALT: 41, AST: 39, total bilirubin: 0.3 (direct: 0.18), serum albumin: 4.3, PT: 1.4, PTT: 40, INR: 1.4, and FBS: 87.

She was receiving Avastin-maintenance therapy (375 mg/month) in addition to VCZ, and broad-spectrum (including linezolid and piperacillin-tazobactam). She continued Avastin-maintenance therapy without any complication after developing PRES and VCZ discontinuation. The patient also received pantoprazole in addition to supplements during her admission. With confidence, VCZ gets the credit for inducing PRES in this case, as bevacizumab (avastin) nor other medications could have led to the development of PRES. The only possible interaction was [VCZ and pantoprazole], which thoroughly discussed in case 1.

References

1. Anastasopoulou S, Eriksson MA, Heyman M, et al. Posterior reversible encephalopathy syndrome in children with acute lymphoblastic leukemia: Clinical characteristics, risk factors, course, and outcome of disease. *Pediatr Blood Cancer*. 2019;66:e27594.
2. Szarfman A, Machado SG, O'neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Safety*. 2002;25:381-392.