Letter

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Clinical characteristics and pharmacokinetics of PAXLOVID in COVID-19 patients with hematological tumor

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To the editor: Since the onset of COVID-19, several new treatments have been studied, but only a few have received approval for clinical use. However, a challenge we still face is that in real-world medical practice, the patient population may differ from those in clinical trials. For instance, prolonged viral elimination has become an issue in immunocompromised patients [1, 2].

The described patients are part of a retrospective cohort study on COVID-19 approved by the ethics committee of Peking University Third Hospital (No. 2023-007-02). Blood samples were collected as part of routine clinical procedures, and the concentration of nirmatrelvir/ritonavir (PAXLOVID) was measured in the pharmacy laboratory using a previously published LC-MS/MS method [3].

Clinical characteristics

Twelve patients were included in the study, with 10 of whom were male. The average age was 59.3 years, and the mean BMI was 24.1. Patient information is presented in Table 1.

Eleven patients were diagnosed with non-Hodgkin's lymphoma (NHL), and one had mixed phenotype acute leukemia (AML and T-ALL). Except for the two chronic lymphocytic leukemia (CLL) patients with abnormally high lymphocyte counts, the average lymphocyte counts for the other NHL patients was 0.64×10^9/L (reference range: $1.1–3.2\times10^9$/L). Eight patients (67 %) experienced a rebound, with a median of 7 days. One patient passed away after 31 days of hospitalization.

Nirmatrelvir concentration and safety

A total of 45 samples from the 12 patients were collected for therapeutic drug monitoring. The mean concentration after 3 h (C_{max}) was found to be 6,440.4±3,208.7 ng/mL, and the mean trough concentration (C_{min}) was measured at 4,684.0±2,754.8 ng/mL.

Two patients experienced liver injury, with their ALT levels increased to 2.2 and 7.5 times the baseline after starting PAXLOVID. In the case of patient 8, ALT levels rose to 194 U/L three days after taking Paxlovid, and their C_{min} reached 12,100.0 ng/mL. This suggests the need for caution regarding safety issues that may arise from the excessive concentration.

According to the drug label, the geometric mean C_{max} of nirmatrelvir, when administered as a single 300 mg dose (with ritonavir) is 2,210 ng/mL, and approximately 2-fold accumulation was observed in the phase I clinical trials, despite the EC90 being only 292 ng/mL [4]. A similar concentration was observed in Chinese healthy volunteers (C_{max} 2,620 ng/mL, single dose) [5]. Therefore, we speculate that in patients, the absorption process of nirmatrelvir may

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Table 1: Patient demographics and clinical characteristics.

ID	Sex	Age, year	Weight, kg	BMI	Hematological comorbidity	Lymphocyte[a] before Paxlovid use, $\times 10^9$/L[a]	COVID-19 severity	Initiation of Paxlovid, days	Viral elimination after 1st cycle Paxlovid use, days	Time to rebound, days	Viral elimination after 2nd cycle Paxlovid use, days	Time from symptom to viral elimination, days	C_{min} of nirmatrelvir, ng/mL[c]	Other COVID treatment[d]	Survival state (3 months)
1	M	64	74	23.9	MCL[e]	0.16	Severe	30[b]	Prolonged positive	/	Prolonged positive	75+	3,530; 4,094	AZV, BAR	Death
2	M	60	78	24.6	MCL[e]	0.17	Severe	18[b]	Negative	10	Negative	53	3,110; 2,963	AZV, BAR	Live
3	M	46	67	22.6	MPAL	0.6	Non-severe	3	Negative	/	/	19	1,240	/	Live
4	M	67	76.5	24.7	MCL	0.49	Severe	22[b]	Negative	11	Negative	46	4,730	AZV, BAR, TOC	Live
5	F	70	49	25.0	MZL	0.33	Severe	26	Negative	7	Negative	39	7,200	BAR	Live
6	M	41	75	26.0	MCL[f]	0.46	Non-severe	16[b]	Negative	12	Negative	36	5,810; 4,760 (C_{25})	AZV	Live
7	M	40	87	26.3	DLBCL[f]	0.54	Non-severe	18	Negative	8	Negative	53	2,670	BAR	Live
8	M	58	77	24.3	CLL	89.36	Severe	11	Negative	8	Negative	42	12,100; 3,265	BAR	Live
9	F	65	58	22.1	FL	0.82	Severe	22	Negative	7	Negative	47	6,442 (1st dose)	BAR	Live
10	M	89	53	18.3	CLL	139.93	Severe	28[b]	Prolonged positive	/	/	62+	6,143	AZV, BAR, TOC	Live
11	M	69	74	26.2	DLBCL	0.47	Severe	22	Negative	6	Prolonged positive	46+	10,378 (C_8)	AZV, BAR	Death
12	M	42	75.5	25.5	FL	2.32	Severe	47[b]	Negative	7	Negative	53	2,277	AZV, BAR	Live

[a]Reference range: 1.1–3.2 $\times 10^9$/L. Record the nearest result before the Paxlovid treatment. [b]Azvudine was used before Paxlovid. [c]Steady-state trough concentration unless otherwise noted. Two C_{min} means collected from different cycle of Paxlovid use. [d]All patients were treated with corticosteroid. [e]Received CAR-T treatment. [f]Received ASCT treatment. BMI, body mass index; MCL, mantle cell lymphoma; MPAL, mixed phenotype acute leukemia; MZL, marginal zone lymphoma; DLBCL, diffuse large B cell lymphoma; CLL, chronic lymphocytic leukemia; FL, follicle lymphoma. CAR-T, chimeric antigen receptor (CAR)-T cell therapy; ASCT, autologous stem cell transplantation; AZV, azivudine; BAR, baricitinib; TOC, toclizumab.

be altered. Studies have indicated that the intestine could also be a target organ of SARS-CoV-2 [6]. Increased intestinal permeability due to the infection could enhance the absorption of nirmatrelvir, leading to higher plasma concentrations in these patients.

Our study's patients exhibited significantly higher nirmatrelvir concentrations compared to clinical trials, with substantial variability among individuals. To better understand the characteristics of the target population and ensure rational drug use, we need further investigation into the pharmacokinetic profiles of these medications. Additionally, no correlation was observed between nirmatrelvir concentration and the duration of viral shedding. Therefore, it is essential to explore the appropriate dosage and dosing regimen in more detail.

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Research ethics: The study was approved by the ethics committee of Peking University Third Hospital (No. 2023-007-02).

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