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LACTIC ACIDOSIS AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION POTENTIALLY RELATED TO LETERMIVIR

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The authors confirm that the PI for this paper is Philippe Hantson and that they had direct clinical responsibility for patients.

Abstract

A 53-year-old woman with a history of acute myeloid leukemia received a second allogenic hematopoietic stem cell transplant (HSCT) and was prescribed, among other medications, acyclovir and letermovir (480 mg daily oral dose) for prophylaxis of respectively herpes simplex and cytomegalovirus infection. The patient was admitted in the intensive care unit (ICU) for dyspnoea and oliguria. Laboratory investigations revealed acute kidney injury, but also a severe and progressive lactic acidosis. Liver function tests were within normal range. The combination of lactic acidosis, hypoglycaemia and acylcarnitine profile in plasma raised the suspicion of mitochondrial toxicity. Letermovir therapy was interrupted and determination of plasma letermovir pharmacokinetics revealed a prolonged terminal half-life (40.7 h) that was not significantly influenced by continuous venovenous hemofiltration. Exploration for genetic polymorphisms revealed that the patient was *SLCO1B1**5/*15 (c.521T>C homozygous carrier and c.388A>G heterozygous carrier) with a predicted non-

functional OATP1B1 protein. The relationship between letermovir accumulation and development of lactic acidosis requires further observations.

Key words: letermovir – hematopoietic stem cell transplantation – pharmacokinetics
SLCO1B1 gene polymorphism – lactic acidosis

1. INTRODUCTION

Letermovir is an inhibitor of cytomegalovirus (CMV) viral terminase that has been approved for prophylaxis of CMV infection and disease in CMV-seropositive allogeneic hematopoietic stem cell transplant (HSCT) recipients. Letermovir is well tolerated in populations with mild to moderate hepatic or renal impairment [1,2]. Letermovir pharmacokinetics may be affected by variants of the solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene and also by some drug-drug interaction, but usually with a limited clinical impact [3,4].

2. CASE REPORT

A 53-year-old woman was admitted in the Intensive Care Unit (ICU) for progressive dyspnea and oliguria. She had a medical past history of acute myeloid leukemia (AML) with inv(16) (CBF-MYH11) and FLT3-ITD and had received a first allogeneic HSCT in May 2020. The patient did not present co-morbidities predisposing to kidney or hepatic injury. A complete remission was obtained and the patient was placed on sorafenib as maintenance therapy. She experienced as early complications a mild form of graft-versus-host-disease (GVHD) (NIH grade 1 for the skin and liver) with a favourable outcome. Unfortunately, a relapse of AML was noted in March 2022 and chemotherapy was initiated with cytarabine followed by gilteritinib as maintenance therapy. She received a second allogeneic HSCT on July 20, 2022 (29 months after

the first transplant). Serum creatinine at baseline was 1.04 mg/dL (0.60-1.30). Febrile neutropenia was already present by the day following transplant. The source was identified as a lower urinary tract infection due to *Enterococcus faecium* and complicated by septicaemia. Treatment started with piperacillin/tazobactam plus vancomycin. As an early complication, the patient also developed cytokine release syndrome. Nine days after HSCT, there was also a decrease in renal function from a mixed origin: cardiorenal syndrome with fluid overload and chemotherapy-related cardiotoxicity. Prophylaxis against herpes simplex and cytomegalovirus included respectively oral acyclovir (400 mg daily, started one week before HSCT and reduced to 200 mg after progression of renal dysfunction) and oral letermovir (480 mg daily since HSCT, started from HSCT for a total of 13 doses). Other medications are listed in Table I. The respiratory condition progressively deteriorated on the hematology ward, together with a decrease in urine output. The patient was admitted in the ICU 13 days after HSCT. On physical examination, the patient was fully conscious with high respiratory rate (45/min), but preserved blood pressure (143/90 mmHg). Laboratory investigations on admission revealed: pH 7.25 (7.35-7.45), pCO₂ 28 mmHg (35-45), bicarbonate 13 mmol/L (22-28), potassium 4.7 mmol/L (3.5-5.0), chloride 92 mmol/L (97-107), lactic acid 5.5 mmol/L (0.5-2.2), anion gap 24.5 mmol/L, serum creatinine 3.16 mg/dL (0.6-1.30) (estimated glomerular filtration rate 16 mL/min/1.73m²), glucose 130 mg/dL (70-100). Liver function tests were within normal range. Echocardiography showed a moderate mitral valve regurgitation with a well preserved left ventricular function. No hemodynamic support was required. The central venous oxygen saturation (ScvO₂) was 61.8%. The abdomen computed tomography (CT) excluded intestinal ischemia. A few hours after ICU admission, the patient experienced hypoglycemic episodes and dextrose 50% was then continuously

infused. The blood 3-hydroxybutyrate concentration was 448 $\mu\text{mol/L}$. The acylcarnitine profile in plasma was altered and revealed increased concentrations of short, medium and long chains as follows: C4:0 0.53 $\mu\text{mol/L}$ (<0.38), C5:0 0.45 (<0.23), C5DC 0.37 (<0.13) , C6:0 0.57 $\mu\text{mol/L}$ (<0.13), C8:0 0.58 $\mu\text{mol/L}$ (<0.21), C10:0 1.52 $\mu\text{mol/L}$ (<0.35), C12:0 0.73 $\mu\text{mol/L}$ (<0.15), C14:1 0.72 $\mu\text{mol/L}$ (<0.18), C16:0 0.82 $\mu\text{mol/L}$ (<0.22) and C18:1 1.24 (<0.41).

In front of an unexplained lactic acidosis and in the absence of recommendation for letermovir following acute kidney injury, this medication was interrupted. Blood was sampled for the determination of plasma letermovir concentration before the start of continuous venovenous hemofiltration (CVVH), 18 hours after the last oral administration. Plasma letermovir was measured using a validated high performance liquid chromatography tandem mass spectrometry method with a lower limit of quantification of 0.1 $\mu\text{g/mL}$. Plasma level was 5300 $\mu\text{g/L}$ and the terminal elimination half-life ($t_{1/2}$) calculated on four consecutive data points was 38.7 hours. Additionally, the blood tacrolimus concentrations rose from 10.5 to 28.8 ng/mL (target range:10-15) by the same day. Evolution of lactate concentrations is illustrated in Figure 1 and letermovir pharmacokinetics in Figure 2. On ICU day 4, the patient had a cardiac arrest due to severe hypoxemia after an episode of major hemoptysis. Refractory status epilepticus developed as the consequence of postanoxic encephalopathy. The patient died on ICU day 6 from this complication that appeared unrelated to lactic acidosis. Genotyping of relevant pharmacogenes revealed that the patient was *CYP3A4**1/*1 (absence of main *CYP3A4* variants including c.522-191C>T defined as *CYP3A4**22), *CYP3A5**3/*3 (*CYP3A5* non expresser, c.219-237A>G homozygous carrier) and *SLCO1B1**5/*15 (c.521T>C homozygous carrier and c.388A>G heterozygous carrier) with a predicted non-functional OATP1B1 protein.

3. DISCUSSION

Among the medications that the patient received at the time of the development of lactic acidosis, none could be clearly associated with this type of complication. In particular, lactic acidosis is generally not a complication of acyclovir therapy, even in the patients who developed acute kidney injury. Some antiviral drugs can induce lactic acidosis, but to date, there was no mention of letermovir. The alterations of the acylcarnitines profile, including the elevation of several lengths of acylcarnitines, together with lactic acidosis and ketone bodies production could suggest a mitochondrial toxicity. Such acylcarnitines profiles are seen in mitochondrial disorders such as multiple acyl-CoA dehydrogenase deficiency.

Letermovir therapy is usually well tolerated, adverse effects include nausea, vomiting and diarrhea. Letermovir is a substrate of CYP3A4/5 and UGT1A1/3 *in vitro*, and an inhibitor of P-gp, OATP1B1 and OATP1B3 [5]. Letermovir is highly protein bound (99%) and no significant elimination should be expected from renal replacement techniques. Renal excretion represents less than 2%, while fecal excretion is reaching 93% (unchanged for 70%). No dose adjustments are recommended for patients with an estimated glomerular filtration rate > 10 mL/min. Due to the lack of data, letermovir is not recommended for patients with end-stage renal disease with or without dialysis [2]. Previous observations have documented elevated drug exposure in renally impaired subjects. During normal therapeutic use, the plasma terminal half-life is 12 hours [5].

There are limited data regarding therapeutic drug monitoring of orally administered letermovir prophylaxis in allogeneic HSCT recipients. In a population of 40 consecutive patients, letermovir trough concentration remained stable during the first 70 days post-HSCT at a median of 286 µg/L (interquartile range, 131 to 591 µg/L), with large inter-

patient/intra-patient variability [4]. Patients who received simultaneously either posaconazole or cyclosporine had higher letermovir trough concentrations. Patients with letermovir-associated adverse effects had also higher trough concentrations. These adverse manifestations mainly involved atrial fibrillation, peripheral oedema, myalgias, and the causality was never firmly demonstrated. No case of lactic acidosis was documented. Other studies coming from the organ transplant literature have shown higher untimed letermovir concentrations, ranging from not detectable to 24,250 µg/L [6]. In a series of 74 letermovir trough samples obtained in patients receiving oral letermovir in real-life conditions, the mean trough concentration was 3397 ± 2531 µg/L [7]. Two patients on renal replacement therapy (RRT) received letermovir intravenously at a dosage of 480 mg daily; one patient had a mean trough level of letermovir 1.7-fold higher than reported in the previous study and did not experience adverse effects. There was no influence of RRT on letermovir concentrations [8]. This apparent discrepancy between the studies in the interpretation of letermovir pharmacokinetics may be explained not only by the large inter-individual and intra-individual variability, but also by the lack of precise timing of blood sampling and differences in testing methods [4,7].

Regarding drug-drug interactions, concomitant use of letermovir and tacrolimus or cyclosporine may result in an increase in trough concentrations of the immunosuppressants by CYP3A inhibition [9]. The pharmacokinetics of fluconazole and letermovir was not significantly changed following co-administration [10]. This was also the case for combined therapy with mycophenolate mofetil [9].

Analysis of the patient's pharmacogenetic profile showed a *CYP3A* genotype expected for a Caucasian population, namely normal *CYP3A4* activity and the absence of *CYP3A5* activity. In contrast, the *SLCO1B1* genotype (*5/*15) corresponds to a

complete absence of OATP1B1 activity and is quite rare in the Caucasian population (c.521T>C, rs4149056, MAF: 0.16; expected frequency of homozygous carriers 2.6% according ensemble.org). The absence of OATP1B1 activity in this patient therefore most likely contributed to the marked increase in letermovir plasma concentrations.

4. CONCLUSION

In conclusion, our observation suggests that higher letermovir trough concentrations and prolonged terminal half-life elimination may be observed in selected HSCT recipients under some conditions of drug-drug interaction and/or altered metabolism and transport. The relationship with the development of otherwise unexplained lactic acidosis remains hypothetical and requires further observations. Therefore, monitoring of letermovir concentrations could be useful in a high-risk population with renal or hepatic dysfunction, or co-medications.

CONTRIBUTORS

B.M. wrote the first version of the manuscript, MC.V. performed the determination of letermovir concentrations, J.D. supervised chemical analysis of acylcarnitine, V.H. conducted genotyping analysis, P.H. and F.L. revised and approved the final version of the manuscript.

COMPETING INTERESTS

No conflicts of interest.

PATIENT CONSENT STATEMENT

The relatives of the patient provided written informed consent to publish this report.

DATA AVAILABILITY STATEMENT

The clinical and analytical data are available from the corresponding author, P.H., upon reasonable request.

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Table I. List of the medications prescribed before the development of lactic acidosis.

Letermovir	Tacrolimus
Acyclovir	Mycophenolate mofetil
Piperacillin/tazobactam	Levothyroxine
Vancomycin	Pantoprazole
Fluconazole	Sertraline

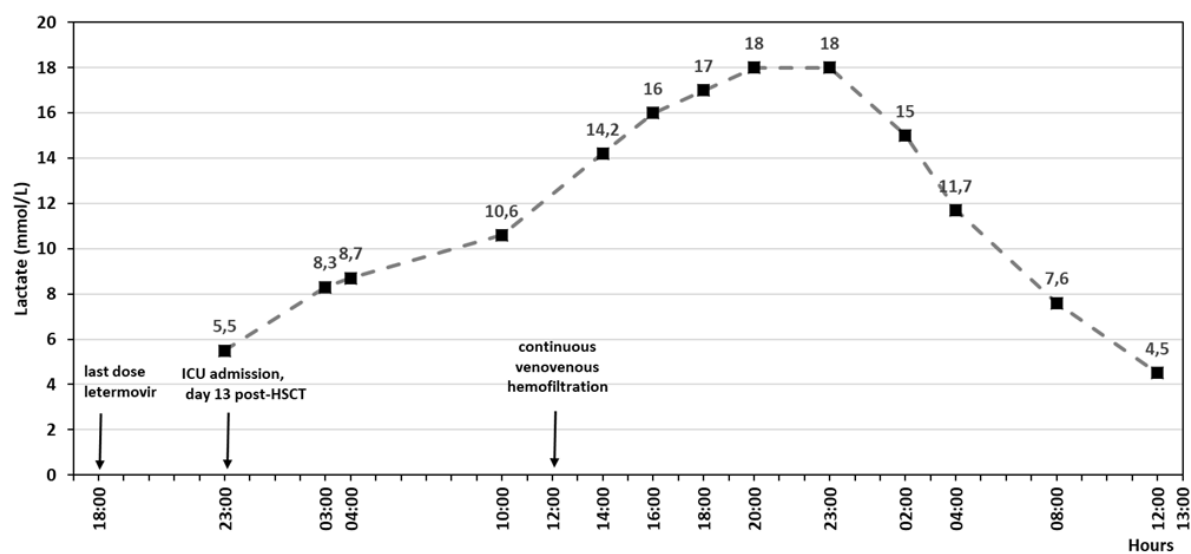


Figure 1. Evolution of lactic acidosis over time.

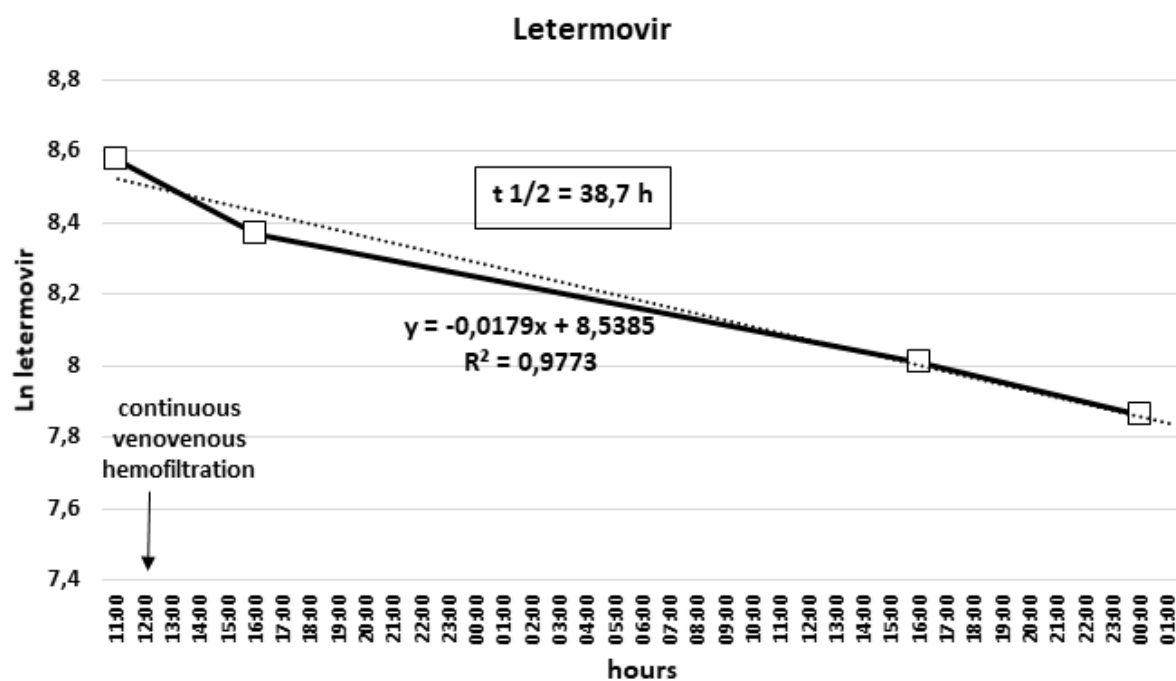


Figure 2. Pharmacokinetics of letermovir, first sample obtained one hour before the start of continuous venonevous hemofiltration and 18 hours after the last oral administration.