

Case report

Dialysate concentration and pharmacokinetics of 2F-Ara-A in a patient with acute renal failure

Kielstein JT, Stadler M, Czock D, Keller F, Hertenstein B, Radermacher J. Dialysate concentration and pharmacokinetics of 2F-Ara-A in a patient with acute renal failure. Eur J Haematol 2005; 74: 533–534. © Blackwell Munksgaard 2005.

Abstract: Fludarabine is frequently used for treatment of B-cell chronic lymphocytic leukemia and in conditioning regimens for hematopoietic cell transplantations. The total body clearance of the principal metabolite 2-fluoro-ara-A (2F-Ara-A) correlates with the creatinine clearance. We report data on total dialysate concentration as well as pharmacokinetics of 2F-Ara-A in a patient with anuric acute renal failure. On three consecutive days the patient received a daily dose of 80 mg (40 mg/m²) fludarabine and underwent three consecutive extended (daily) dialysis (ED) sessions. ED removed a considerable amount of the drug. The average dialysis clearance was 33.85 ml/min which is about 25% of the clearance in patients without renal failure. No toxic side effects of the treatment were observed. This case suggests that fludarabine treatment can be considered in patients requiring dialysis if dose reduction and adequate removal of the drug by hemodialysis is provided.

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Key words: Fludarabine; pharmacokinetics; acute renal failure; GENIUS-system; extended (daily) dialysis (ED).

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Accepted for publication 4 February 2005

Fludarabine, a fluorinated nucleoside analog of the antiviral agent vidarabine, 9-(beta)-D-arabinofuranosyladenine (ara-A) is frequently used in patients with B-cell chronic lymphocytic leukemia refractory to standard alkylating agent containing regimens. Ara-A is also used in conditioning regimens for non-myeloablative stem cell transplantations (1). Fludarabine phosphat (MW 365.2) is a pro-drug that is rapidly dephosphorylated to 2-fluoro-ara-A and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP (2). The *in vitro* protein binding ranges between 19% and 29%. Although the mechanism of action is not completely characterized, this metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. The total body clearance of the principal metabolite 2-fluoro-ara-A correlates with the creatinine clearance, and the renal clearance represents approximately 40% of the total body clearance. Patients with moderate renal impairment

(17–41 mL/min/m²) receiving 20% reduced fludarabine dose had a similar exposure (AUC; 21 vs. 20 nM h/mL) compared to patients with normal renal function receiving the recommended dose (3). So far, there are no published data on the effect of hemodialysis on the pharmacokinetics of fludarabine.

We report data on total dialysate content as well as pharmacokinetic data on the main fludarabine metabolite (2F-Ara-A) in a 49-year-old patient. He developed anuric acute renal failure and underwent extended dialysis (ED) in the intensive care unit (ICU). This new hybride technique is increasingly used since it combines excellent detoxification with cardiovascular tolerability, even in severely ill patients in the ICU (4). The patient received fludarabine conditioning for a second attempt of autologous reconstitution for repeated graft failure after unrelated allogeneic stem cell transplantation for agnogenic myeloid metaplasia. On three consecutive days the patient received a daily dose of 80 mg (40 mg/m²) fludarabine via infusion pump

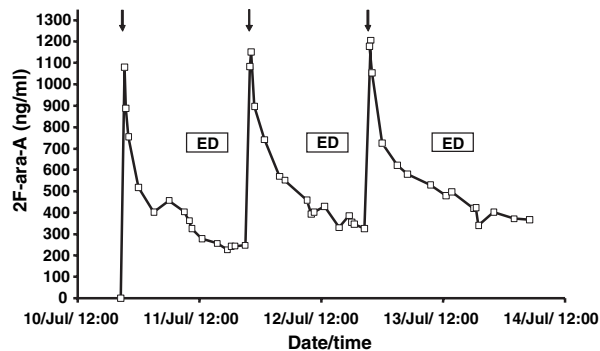


Fig. 1. Plasma concentrations of 2F-Ara in a patient with acute renal failure undergoing ED. Width of the boxes indicates the duration of ED. Administration of Fludarabine is indicated by the arrows.

over a period of 30 min. Twelve hours after each infusion the patient received an 8 h ED using the GENIUS batch dialysis system (Fresenius Medical Care, Germany). A high-flux hollow-fiber dialyzer was used (F60S®; 1.3 m², Fresenius Medical Care, Germany). Blood flow and countercurrent dialysis fluid flow was 160 mL/min. Blood samples were drawn before and after administration of the drug, before and during dialysis, at the end of the treatment as well as after ED treatment as indicated in Fig. 1. Total drug removal was assessed by measuring drug concentration in the spent dialysate. Since the entire dialysis fluid is contained in a 75-L glass container the GENIUS-system permits easy access to the entire amount of substances that have been removed during a dialysis session (5). The concentration of 2F-Ara-A over time is depicted in Fig.1. Using standard software WinNON-LIN, the pharmacokinetic parameters that have been calculated for each of the three-dialysis sessions are shown in Table 1. For three doses a bi-exponential decay profile of 2F-Ara-A, with a fast α phase (1.5, 1.8, and 3.3 h) and a slow β phase (19, 21, and 26 h) was demonstrated. Due to accumulation, elimination time, mean retention time and area under the curve increased after each dose.

The clearance without dialysis was calculated to be 1.87 L/h/m², which is 46% of the clearance reported for patients without renal impairment (4.08 L/h/m²). The dialysate concentration of 2F-Ara-A after one ED treatment was 94.2 ng/mL yielding a total amount in the dialysate of 7 mg. The average dialysis clearance was 1.02 L/h/m², which is about 25% of the clearance in patients

Table 1. Pharmacokinetic parameters for each of the three slow low flow hemodialysis sessions

Parameter	Unit	ED 1	ED 2	ED 3
$t_{1/2}$	h	15.3	22.3	24.4
AUC _{0-t_{last}}	μmol/L*h	33.6	41.8	71.5
CL	mL/min	72.7	48.8	37.9
MRT	h	22.0	30.6	34.6
V _d	L	96.0	90.4	80.0
AUC/dose	μmol/L*h	154	191	327
T _{last}	h	24.5	23.3	47.0

ED: 1–3; $t_{1/2}$, serum elimination half-life; AUC_{0-t_{last}}, area under the curve; CL, total clearance; MRT, mean residence time; V_d, volume of distribution; T_{last}, time of last measured concentration.

without renal failure. Unfortunately the patient, who was in persistent aplasia due to repeated graft failure after unrelated allogeneic stem cell transplantation, died due to septic complications before an effect of the treatment on myelosuppression could have been evaluated.

This case suggests that fludarabine can be considered in patients on dialysis if dose reduction and adequate removal of the drug by hemodialysis is provided. Further studies on the pharmacokinetics of fludarabine in patients with a clearance < 30 mL/min are needed.

Acknowledgements

We thank the Department of Pharmacokinetics at SCHERING AG, Germany, for the measurement of 2F-Ara-A concentrations.

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