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ORIGINAL ARTICLE

Effective clearance of Ara-U the major metabolite of cytosine arabinoside (Ara-C) by hemodialysis in a patient with lymphoma and end-stage renal failure

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Abstract
Purpose We report that hemodialysis clears Ara-U from the blood after high-dose Ara-C treatment in a patient with lymphoma and end-stage renal failure.
Methods The patient received two doses of Ara-C 1 g/m^2 24 h apart and was hemodialyzed at about 6 h after each dose and subsequently as per her usual dialysis schedule. Multiple blood samples were collected after dosing. Blood and dialyzate were also collected from the dialysis circuit during a second identical treatment cycle. Ara-C and its metabolite Ara-U in plasma and dialyzate were measured chromatographically, and the data subjected to pharmacokinetic analysis.
Results The distribution and elimination half-lives, steady-state volume of distribution and clearance values were 0.5 h, 7 h, 181 L and 307 l/h for Ara-C and 4.1 h, 34 h, 118 L and 2.64 l/h for Ara-U, respectively. The dialysis sessions immediately after the first and second doses cleared 39 and 52% (as Ara-U) of the respective Ara-C doses. Some 63% of Ara-U in plasma was extracted by dialysis. The patient showed no signs of neurotoxicity or other drug-related adverse effects.
Conclusion Hemodialysis is very effective in clearing Ara-U from the plasma in renal failure, and this maneuver could easily be used routinely to prevent Ara-U accumulation and minimize adverse effects in patients with renal failure.

Keywords Cytarabine · Ara-C · Ara-U · Renal failure · Dialysis · Pharmacokinetics

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Introduction

A previous report [1] suggested that following use of high-dose Ara-C, accumulation of Ara-U in the plasma and CSF of patients with renal insufficiency may be responsible for an associated higher incidence of neurotoxicity [2, 3] via elevation of Ara-U concentration in plasma and CSF [2, 4]. There is one report in a child with lymphoma showing that both Ara-C and Ara-U can be cleared by hemodialysis or hemofiltration [5]. Given the perceived need to minimize Ara-U accumulation, we have documented the plasma and dialyzate disposition of both Ara-C and Ara-U in a patient who received high-dose Ara-C and was also hemodialyzed.

Patients and methods

Case

The patient is a 48-year-old woman with relapsed Stage IVA mantle cell lymphoma on a background of dialysis-

dependent end-stage renal failure. Initially diagnosed with mantle cell lymphoma 2.5 years prior, she was treated with six cycles of a modified R–CHOP regimen (rituximab, cyclophosphamide, doxorubicin and prednisolone) with omission of the vincristine. A complete remission was achieved with the clearance of lymphoma cells from blood and bone marrow and resolution of lymphadenopathy.

The patient re-presented with relapsed mantle cell lymphoma as diagnosed by progressive splenomegaly and the presence of lymphoma cells in blood and bone marrow. Therapy consisted of Ara-C 1 g/m^2 with the patient's body surface area capped at 2 m^2 due to obesity (height 1.66 m, weight 111 kg). Following 3-cycles of single agent Ara-C, a partial response was achieved with a reduction in splenic size and fewer peripheral blood circulating lymphoma cells. No neurotoxicity or unexpected toxicities occurred with Ara-C treatment. Given the partial response, treatment with Ara-C and carboplatin has been commenced with a view to a future autologous stem cell transplant.

Ara-C (Cytarabine injection, Pfizer [Perth] Pty Ltd, Australia; 2 g) was administered as a 2 h i.v. infusion and repeated 24 h later. Five 4-hour dialysis sessions (Fresenius FX-80 filter, modified multiBic Hemofiltration Solution at 800 ml/min [48 l/h] and blood flow 300 ml/min [18 l/h], Fresenius Medical Care, Buzen City, Japan) were carried out starting 5.5, 30, 69.5, 141.5 and 189.5 h after the first dose of Ara-C. The first two of these sessions were timed to be 3.5 and 2 h after the end of the infusion of the first and second doses of Ara-C, respectively, so that only Ara-U would be dialyzed. The timing of dialysis reflects the pharmacokinetic profile of Ara-C whereby Ara-C levels are low in blood after 2 h. Blood samples for analysis of Ara-C and Ara-U (2 ml, nominally at 0, 0.3, 0.5, 1, 2, 4, 5, 6, 8, 9, 12 h after the first and second doses, and at 2, 2.5, 3, 4, 5, 6 and 7 days after the first dose) were collected into heparinized tubes containing 1 μg of the cytosine de-aminase inhibitor tetrahydrouridine [6].

For logistic reasons, samples of dialyzate were not able to be collected during the aforementioned treatment cycle. However, on a subsequent identical treatment cycle, samples of blood from the dialysis input and output lines (2 ml) and effluent dialyzate (5 ml, with tetrahydrouridine as before) were collected from the dialysis circuit at approximately 0.2, 0.5, 1, 2, 3 and 4 h after the start of the 1st dialysis session (starting 4.5 h after infusion end) and at 0.4 h, 1, 2, 3 and 4 h after the start of the 2nd dialysis session (starting 4.6 h after infusion end). All samples were placed on ice at 4°C immediately after collection. Blood samples were centrifuged at 1,800*g* for 10 min to separate the plasma. Both plasma and dialyzate samples were then stored at −20°C until analyzed.

Assay of Ara-C and Ara-U by high-performance liquid chromatography (HPLC)

Ara-C, Ara-U and tetrahydrouridine were obtained from Sigma Chemicals, Castle Hill, Australia. Plasma samples (1 ml) were ultrafiltered (Amicon Centrifree® YM-30, Millipore Corp, Billerica, MA, USA), and Ara-C and Ara-U concentrations were analyzed by ion-pair HPLC using the method of Burk et al. [7] with minor modifications. The intra-day relative standard deviations for the assay were 6 and 1.1% for Ara-C at 0.1 and 4 mg/l, respectively and 2.9 and 1.8% for Ara-U at 1 and 40 mg/l, respectively. The limits of quantitation were 0.04 and 0.2 mg/l for Ara-C and Ara-U, respectively. For dialysis fluid, 60-μl samples were injected directly onto the HPLC as before. The limit of quantitation was 0.05 mg/l for Ara-U, while the limits of detection were 0.04 mg/l for Ara-C and 0.02 mg/l for Ara-U.

Pharmacokinetic analysis

One- and two-compartment models with an infusion input were fitted to the plasma concentration (y)-time data sets for Ara-C and Ara-U using the pharmacokinetic program Topfit, Ver 2.0 [8]; weightings of unity and 1/y were investigated. A three-compartment model was also investigated for Ara-U. Goodness of fit of the model to the data was assessed using the model objective function, the Akaike information criterion value and the distribution of residuals. The distribution and elimination half-lives ($t_{1/2}$), area under the plasma concentration–time curve $AUC_{0-\infty,}$ (first dose), volume of distribution at steady-state (V_{ss}) and the clearance (CL) were calculated as previously described [8]. The maximum concentration (C_{max}) was interpolated from the primary data. The plasma extraction ratio for Ara-U during dialysis was calculated as $(C_{input}–C_{output})/C_{input}$, where C_{input} and C_{output} are the respective plasma input and output concentrations of Ara-U.

Results

The concentration–time profiles for Ara-C and its metabolite Ara-U are shown in Fig. 1. Concentrations of both drugs increased rapidly during the infusion and then fell in a biphasic manner. For Ara-C, C_{max}'s were 3.18 and 2.64 mg/l at 0.5 and 2 h after the first and second doses, respectively. For Ara-U, C_{max}'s were 24.8 and 37.3 mg/l, both at 3 h after dose. A two-compartment model best represented the disposition of both the Ara-C (weighting = 1/y) and Ara-U (weighting = 1) data sets. For Ara-C, distribution and elimination $t_{1/2s}$, $AUC_{0-\infty}$, V_{ss} and CL were 0.05 h, 0.7 h, 6.52 mg h/l, 181 L and 307 l/h,

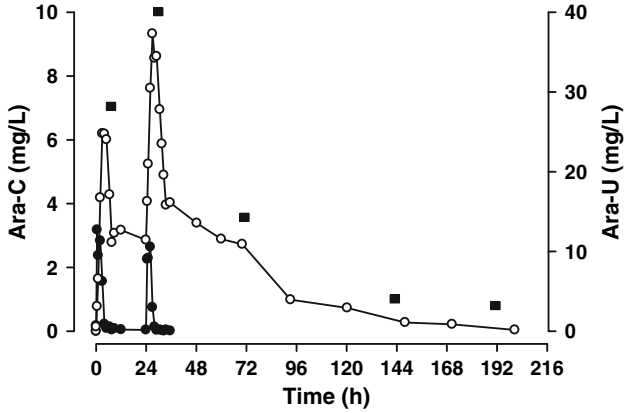

Fig. 1 Plasma concentration–time profile for Ara-C (*closed circles*, *left axis*) and its metabolite Ara-U (*open circles*, *right axis*) following 2 h infusions of 2 g Ara-C at zero and 24 h. Four hourly periods of dialysis are shown by the horizontal *black boxes*

respectively. For Ara-U, distribution $t_{1/2}$, elimination $t_{1/2}$, $AUC_{0-\infty}$, V_{ss} and CL (assuming quantitative formation from Ara-C) were 4.1 h, 34 h, 757 mg h/l, 118 L and 2.6 l/h, respectively.

In the subsequent identical treatment cycle where the dialysis circuit was investigated, Ara-C was below the limits of detection in both plasma and dialyzate samples. The Ara-U concentrations in these samples (Table 1) show a marked plasma input–output concentration gradient with a mean (SD) extraction ratio of 0.63 ± 0.05 (63%). The dialyzate contained mean concentrations of 4 mg/l and 5.4 mg/l during the first and second dialysis sessions, respectively. With a dialyzate flow rate of 48 l/h over 4 h, this equates to a recovery of approximately 773 mg (39% of first Ara-C dose), and 1042 mg (52% of second Ara-C dose) of Ara-U, respectively in the dialyzates.

Discussion

The pharmacokinetic parameters calculated for our study must be considered as "apparent", given that they characterize drug removal by the patient's normal clearance mechanisms as well as by dialysis. For Ara-C, the bi-exponential disposition profile, distribution and elimination $t_{1/2's}$, V_{ss} and CL values were in the same range as those in previous studies [1, 9]. For Ara-U, we observed a bi-exponential disposition, whereas two previous studies have reported mono-exponential disposition [1, 9]. The elimination $t_{1/2}$ of 34 h in our patient was much longer than means of 1.46 and 3.77 h reported in patients with normal renal function [1, 9], but closer to the mean (range) 75 (48–123) h in patients with renal impairment [1].

Ara-U, a small water soluble molecule not bound to plasma proteins, was effectively cleared (39 and 52%) during the first two dialysis sessions. Dialysis using polysulfone membranes has been reported to clear 40–50% of water soluble drugs such as vancomycin and cefepime [10, 11]. The plasma concentrations of Ara-U were high when the first two dialysis sessions commenced and fell rapidly with an apparent distribution $t_{1/2}$ of 4 h during the period of dialysis. Subsequently, the elimination $t_{1/2}$ of Ara-U was much longer at around 34 h. During the latter period, three periods of dialysis were associated with much smaller, but still discernible (Fig. 1) decreases in plasma Ara-U. Hence, we suggest that the short distribution $t_{1/2}$ is largely a result of the dialysis, while the longer elimination $t_{1/2}$ reflects a combination of clearance by dialysis as well as by the patient's limited renal function. It should be noted that previous studies where dialysis was not used [1, 9] did not report a biphasic elimination for Ara-U, supporting the suggestion that the short distribution $t_{1/2}$ we observed is via

Table 1 Ara-U disposition in plasma and dialyzate during 4 h dialysis sessions following two sequential daily doses of Ara-C

Time after start of infusion (h)	Time after start dialysis (h)	Ara-U in input plasma (mg/l)	Ara-U in output plasma (mg/l)	Ara-U in dialyzate (mg/l)	Extraction ratio
Session 1					
6.50	0.17	21.9	7.0	NS[a]	0.68
6.83	0.5	18.7	6.7	5.1	0.64
7.33	1	17.7	5.8	5.0	0.67
8.33	2	13.9	4.7	4.7	0.67
9.33	3	11.8	3.8	3.0	0.67
10.33	4	9.9	3.2	2.4	0.68
Session 2					
7.10	0.43	27.3	11.0	6.4	0.60
7.62	0.95	25.1	9.2	7.5	0.63
8.65	1.98	18.8	9.0	5.4	0.52
9.62	2.95	15.5	6.8	4.3	0.56
10.62	3.95	13.5	5.5	3.5	0.59

[a] *NS* no sample

dialysis clearance. In our study, Ara-C would not be expected to be seen in dialysis fluid, given its low plasma concentrations and its limit of detection in dialyzate.

We have shown that hemodialysis using a contemporary high-flow polysulfone membrane on average extracts 63% of plasma Ara-U. A clearance of 11.7% can be calculated for the only other report of dialysis extraction of Ara-U using an older relatively low-flow polysulfone membrane [5]. In our view, dialysis should be started about 4–5 h after the end of Ara-C infusion, so that its efficacy is not compromized. Ara-C use was not associated with neurotoxicity or other unexpected adverse events in this case.

Definitive studies linking Ara-U accumulation with neurotoxicity have not been performed. The association between neurotoxicity and renal impairment has been established, as has the relationship between renal impairment and elevated levels of Ara-U. However, recent case reports have identified neurotoxicity associated with intrathecal administration of liposomal Ara-C [12, 13], which has low levels of Ara-U in the CSF [14]. Further studies are required to investigate the association between Ara-U accumulation and neurotoxicity.

In our study, we have proven that hemodialysis effectively clears Ara-U and has the potential to minimize neurotoxicity that may result from high Ara-U exposure in patients with renal impairment.

Conflict of interest statement None.

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