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The Clinical Pharmacology of Cytosine Arabinoside

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A. Introduction

There is now little doubt that a proportion of patients with adult acute myelogenous leukaemia will achieve long-term survival and possibly cure with combination chemotherapy. Cytosine arabinoside (araC) is one of the most important drugs used in the treatment of this disease. Despite extensive clinical experience over the past 15 years, the schedule of administration remains controversial. These studies were conducted in an attempt to provide a greater understanding of the effect of both the schedule and route of administration on the clinical pharmacology of araC.

The S phase specificity of araC has led most workers to administer it by continuous intravenous infusion. The potential therapeutic advantages of this schedule have to be balanced against the disadvantages of hospitalisation and the medical and nursing supervision required to maintain continuous intravenous therapy. Some investigators have therefore used subcutaneous bolus injection of araC as a practical alternative to intravenous infusion [1, 12]. The rationale for this was based on the convenience to the patients and the suggestion that following subcutaneous bolus injection araC declined with a half-life of several hours [4]. Methodological problems made this report difficult to assess, and a study was therefore conducted to compare the pharmacokinetics of subcutaneous bolus araC with intravenous bolus and intravenous infusion [13].

Continuous subcutaneous infusion has been successfully used for continuous administration of insulin [10] and desferrioxamine [7], and this route was examined as another alternative to intravenous infusion.

The recent use of massive doses of araC has resulted in a surprisingly high remission rate in patients with acute leukaemia resistant to araC in conventional doses, and may provide a means of overcoming such resistance [3, 8]. The prophylaxis and treatment of central nervous system leukaemia usually requires intrathecal chemotherapy. Patients with neoplastic meningitis may, however, have significant abnormalities of flow which can prevent the even distribution of cytotoxic drugs administered by the lumbar route and may also contribute towards neurotoxicity [5]. Repeated lumbar punctures are often extremely unpleasant for patients. It would clearly be to the advantage of the patient if it were possible to produce prolonged cytotoxic levels of araC in the CSF with the same intravenous therapy used to control the systemic disease. Ho et al. [6] and Canellos et al. [2] have demonstrated that araC crosses the blood-brain barrier during continuous intravenous infusion of conventional doses. It seemed likely that the use of high doses of araC would result in greater CSF araC concentrations than conventional dose infusions, and that these might therefore be useful therapeutically in the treatment of central nervous system leukaemia. The relationship between CSF and plasma levels of araC during high-dose intravenous infusions was therefore studied.

B. Materials and Methods

Patients with acute leukaemia and high-grade non-Hodgkin's lymphoma receiving remission induction or consolidation therapy have been studied. Plasma and CSF araC concentrations were measured using a specific and sensitive radioimmunoassay [9].

C. Results

I. Subcutaneous Bolus araC

The results of this study showed that subcutaneous bolus araC was rapidly absorbed and then declined with a half-life similar to that of intravenous bolus injection. Plasma araC concentrations following a sub-

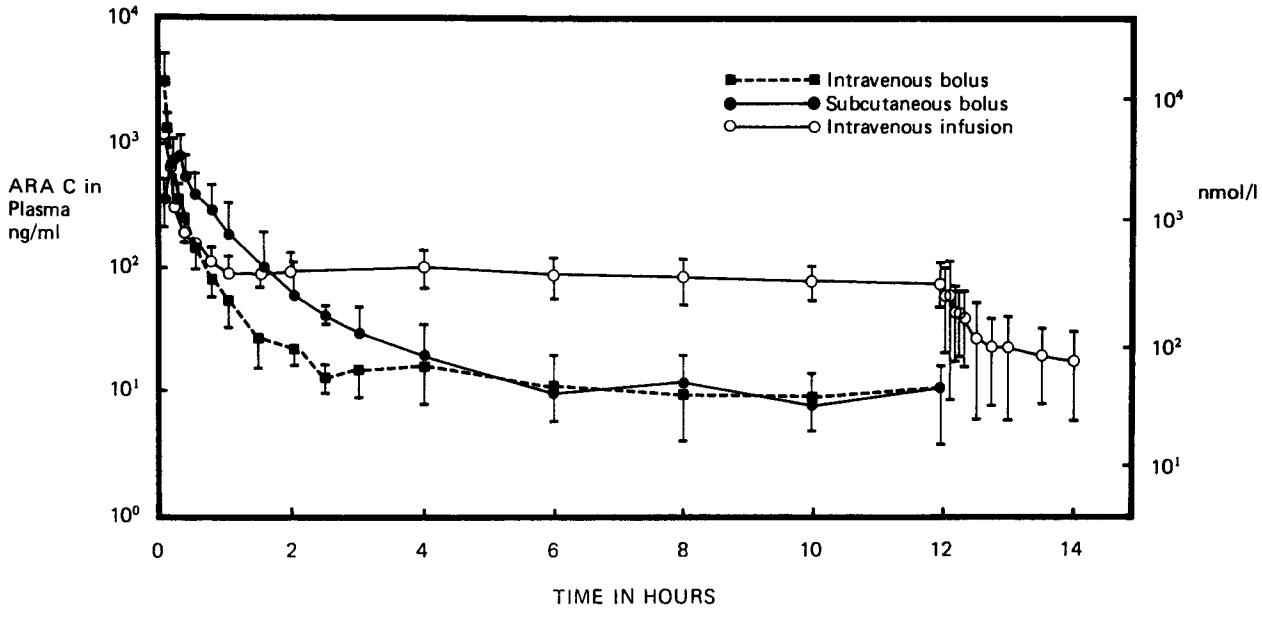

Fig. 1. Mean plasma concentrations (±SD) after intravenous bolus, subcutaneous bolus, and intravenous infusion of araC in five patients

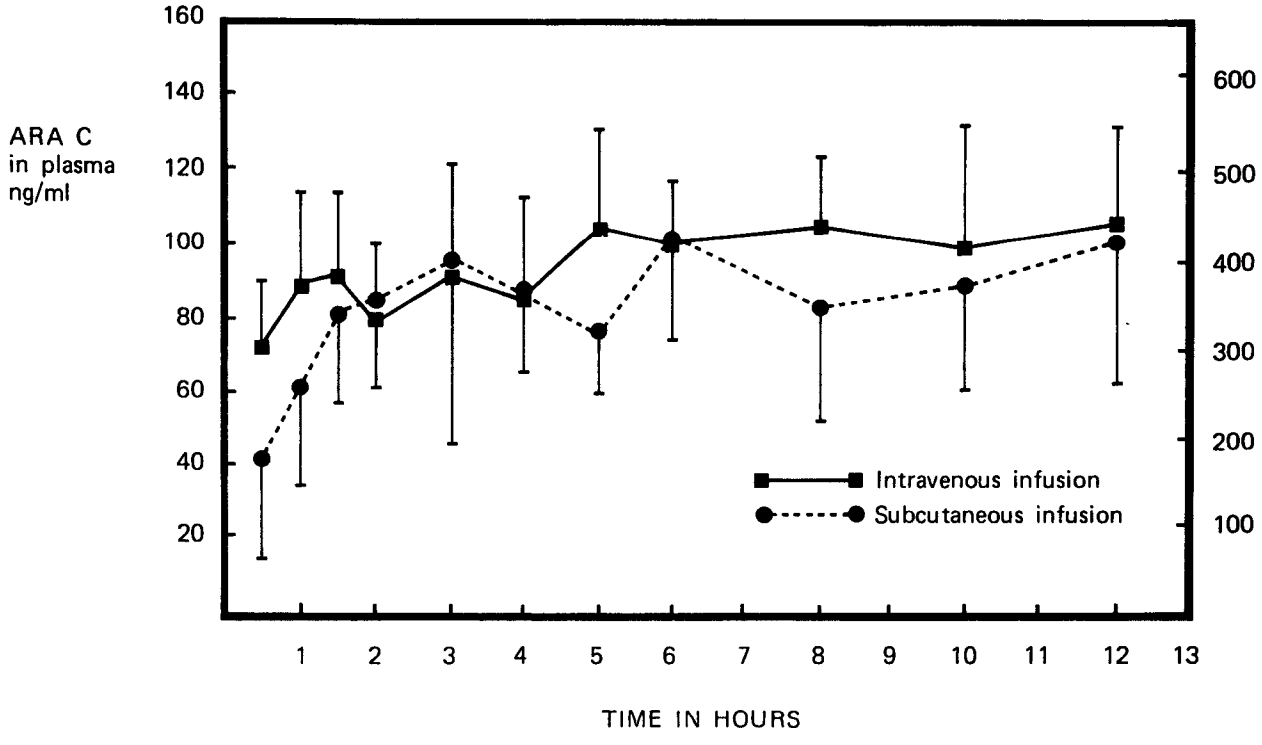

Fig. 2. Mean plasma concentrations ±SD in six patients treated with araC 100 mg/m² by intravenous and subcutaneous infusion over 12 h

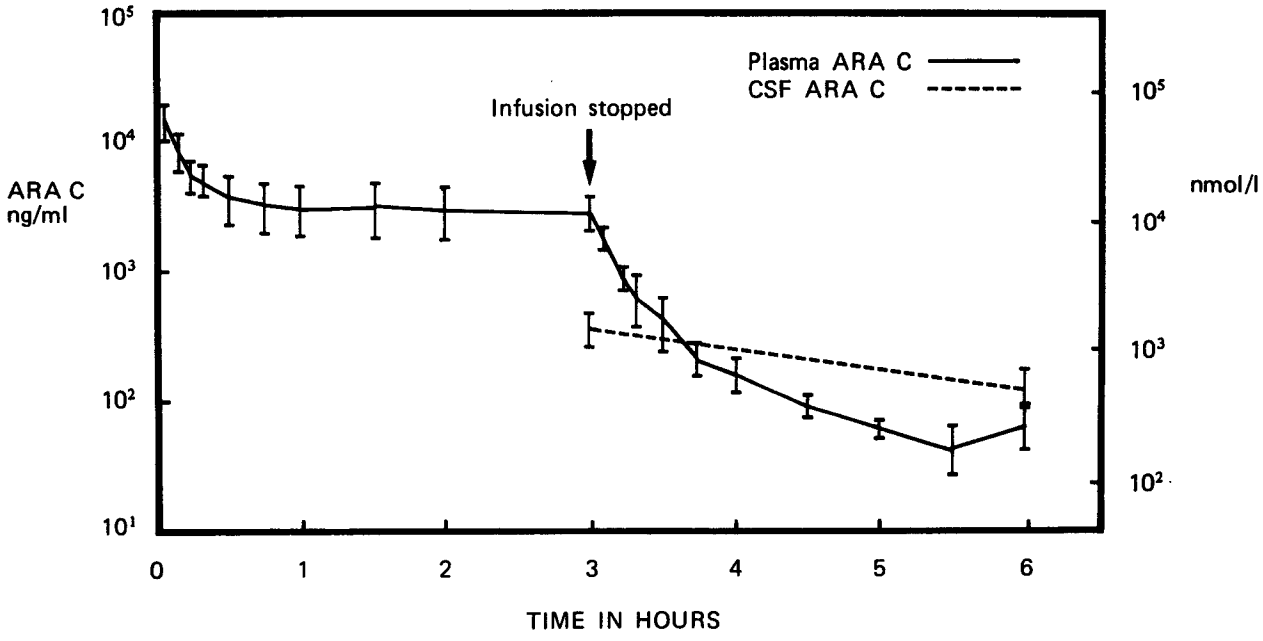

Fig. 3. Mean plasma and CSF levels of araC (±SD) in five patients during an intravenous infusion of 1 g/m² araC over 3 h (one-third of total dose given as a bolus)

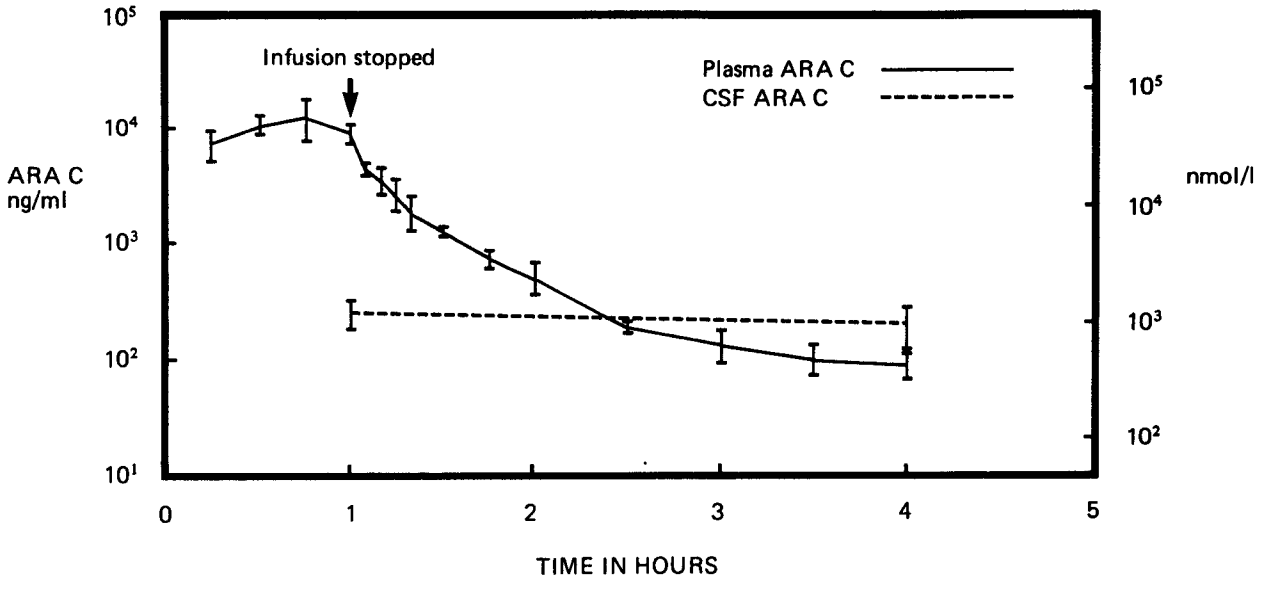

Fig. 4. Mean plasma and CSF levels of araC (±SD) in five patients during an intravenous infusion of 1 g/m² araC over 1 h

cutaneous bolus were greater than those following intravenous bolus only during the first new hours, and within 5 plasma araC concentrations were only 10% of steady state infusion levels (Fig. 1).

II. Subcutaneous Infusion of araC

It was demonstrated that subcutaneous infusion of araC was equivalent to intravenous infusion, and that the time to achieve a plateau, the steady state levels, and the area under the curve were similar for both methods of administration (Fig. 2). There was no local excoriation.

III. High-Dose araC

The relationship between CSF and plasma levels of araC during high-dose infusions was studied. These studies demonstrated that significant concentrations of araC are found in the CSF during therapy with high-dose araC and that levels are similar

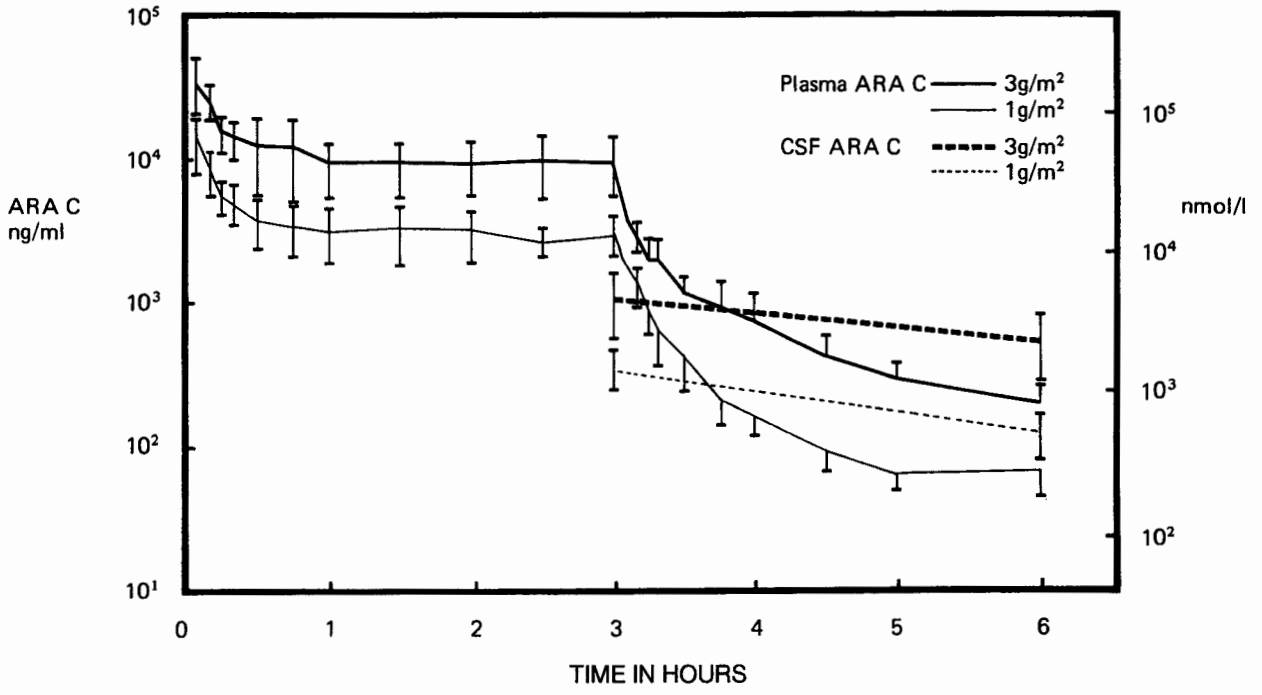

Fig. 5. Mean plasma and CSF concentrations of araC in five patients treated with an intravenous infusion of 1 g/m² and five patients treated with an intravenous infusion of 3 g/m² over 3 h

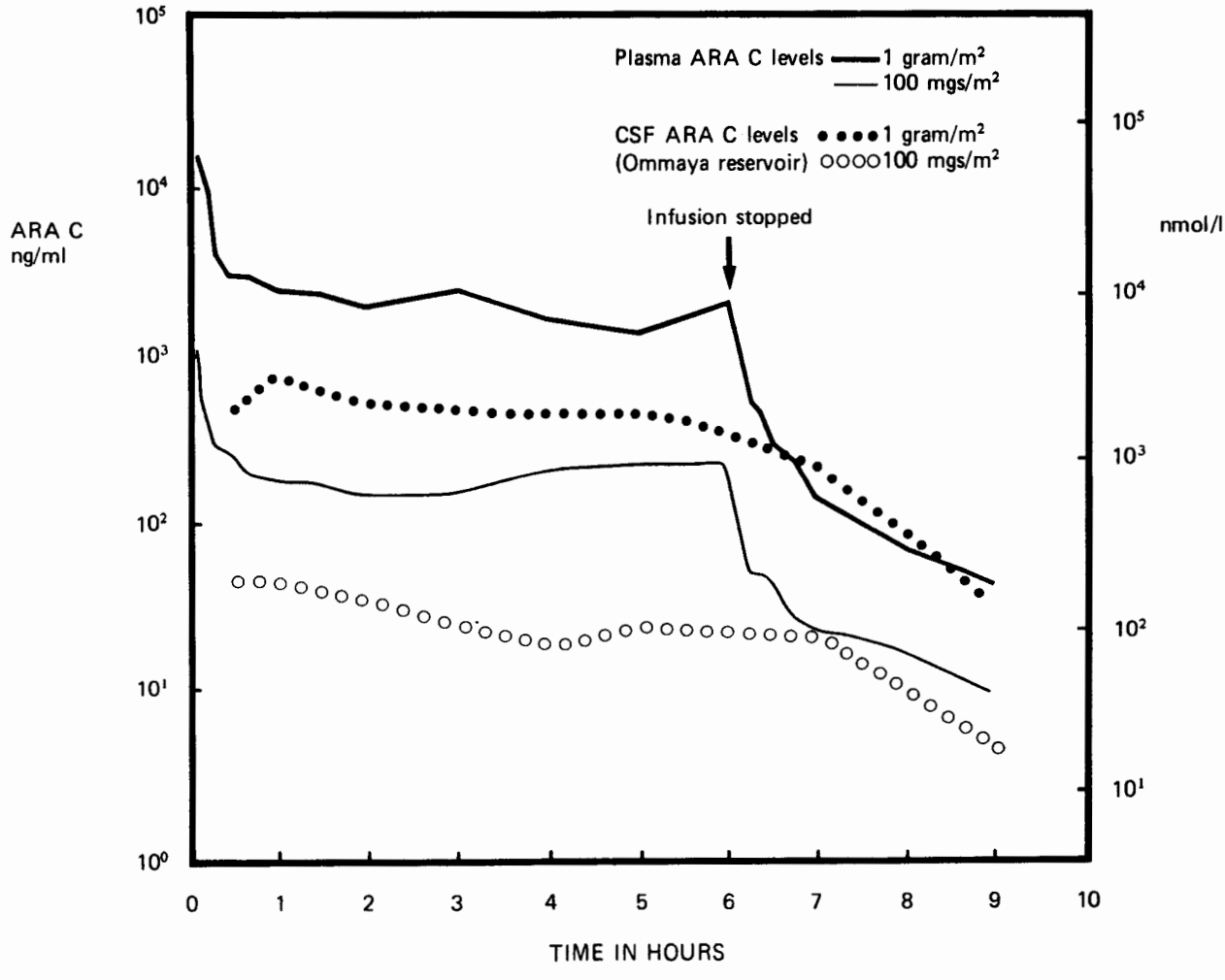

Fig. 6. Plasma and CSF levels of araC in a patient with an Ommaya reservoir treated with an intravenous infusion of 100 mg/m² and 1 g/m² araC over 6 h

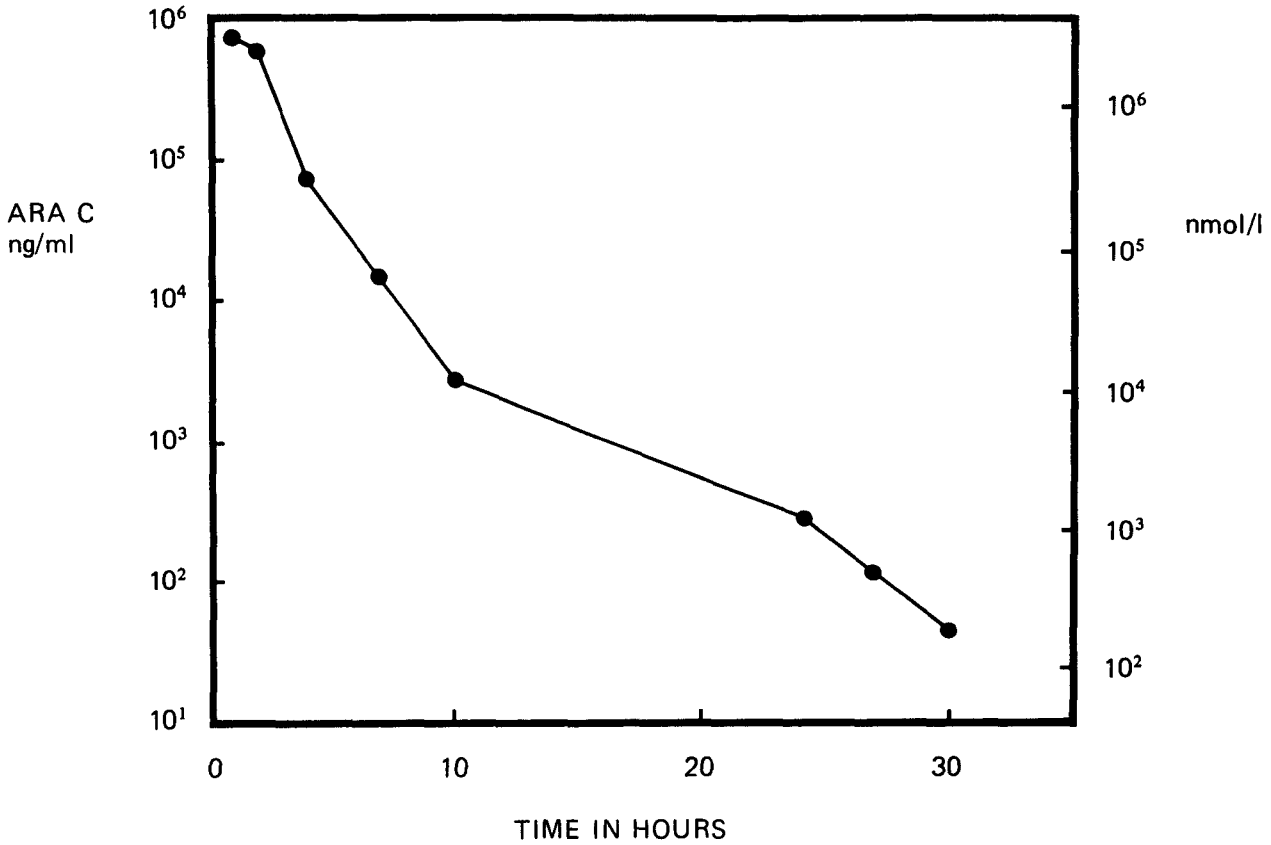

Fig. 7. CSF levels of araC following injection of araC (50 mg/m²) into an Ommaya reservoir

during both 1- and 3-h infusion (Figs. 3, 4). However, the peak plasma concentrations were much greater during the shorter infusions, resulting in a CSF: plasma araC ratio of only 0.03 compared to a ratio of 0.12 during the 3-h infusion. The plasma and CSF araC concentrations during infusions of 3 g/m² were proportionately higher than those found during infusions of 1 g/m² (Fig. 5). Following completion of the infusions, CSF araC levels declined much more slowly than those in plasma with a half-life in excess of 2 h.

The studies conducted in the patient with an Ommaya reservoir (Fig. 6) showed rapid equilibration between plasma and CSF araC, and suggested that araC crossed the blood-brain barrier as effectively during high-dose infusions as at conventional dosage. The CSF concentrations of araC following 50 mg/m² injected into an Ommaya reservoir are shown in Fig. 7. The peak concentrations are several hundred times greater than those found in the CSF during high-dose intravenous therapy, but shortly after 24 h the concentrations have fallen below 100 ng/ml.

D. Discussion

These studies demonstrate that it is not possible to achieve steady state plasma levels of araC comparable to intravenous infusion with the same total dose given by twice or thrice daily subcutaneous bolus injection. Recent data from the CALGB [11], however, showed a significantly longer duration of remission in those patients with acute myelogenous leukaemia who received subcutaneous bolus rather than intravenous bolus maintenance. This suggests that even relatively minor differences between intravenous and subcutaneous bolus araC might significantly affect patient outcome.

Subcutaneous infusion of araC was well tolerated by the patients without local discomfort or excoriation. It is a feasible alternative, and is comparable to intravenous infusion. It allows the patients the advantages of out-patient therapy whilst preserving their venous access.

It is likely that in patients treated with high-dose araC at a dose of 3 g/m² given as a short infusion repeated 12-hourly, CSF

levels >100 ng/ml would be maintained almost continuously. CSF araC concentrations during high-dose therapy are therefore greater than those found in the plasma of patients treated with continuous intravenous infusion at a dose of 200 mg/m² over 24 h. These data suggest that high-dose araC should provide effective therapy for central nervous system leukaemia, and overcome any potential maldistribution of araC in the CSF of patients with leukaemic meningitis.

The central nervous system toxicity associated with high-dose araC cannot be explained in terms of the peak levels achieved in the CSF, as these are considerably lower than those found following intrathecal araC administration. The CNS toxicity is thus most probably related to the prolonged exposure to relatively high CNS concentrations of araC that occur during this therapy.

The most effective schedules of araC administration for both systemic disease and central nervous system leukaemia remain unknown. It is hoped that a greater understanding of the clinical pharmacology will help in the design of studies intended to answer these questions.

References

1. Bell R, Rohatiner AZS, Slevin ML, Ford JM, Dhaliwal HS, Henry G, Birkhead BG, Amess JAL, Malpas JS, Lister TA (1982) Short-term therapy for acute myelogenous leukaemia. Br Med J 284:1221
2. Canellos GD, Skarin AT, Ervin T, Weinstein H (1979) A chemotherapeutic approach to CNS lymphoma and leukaemia by the systemic administration of high dose of antimetabolites. In: Whitehouse JMA, Kay HEM (eds) CNS complications of malignant disease. pp 142–147
3. Early AP, Preisler HD, Slocum H, Rustum YM (to be published) A pilot study of high-dose cytosine arabinoside for acute leukaemia and refractory lymphoma. Clinical response and pharmacology. Cancer Res
4. Finklestein JZ, Scher J, Karon M (1970) Pharmacologic studies of tritiated cytosine arabinoside in children. Cancer Chemother Rep 54:35–39
5. Grossman S, Thompson G, Trump D (1981) Cerebrospinal fluid (CSF) flow abnormalities in patients with neoplastic meningitis (NM). Proc Am Soc Clin Oncol 22:382
6. Ho DHW, Frei E (1971) Clinical pharmacology of 1-B-D-Arabinofuranosylcytosine. Clin Pharmacol Ther 12:944–954
7. Jeffreys DB, Pickup JC, Haw CM, Keen H (1979) Subcutaneous desferrioxamine infusion for haemachromatosis. Lancet II (8156/7):1364–1365
8. Karanes C, Wolfe SN, Herzig GP, Phillips GL, Lazarus HM, Herzig RH (1980) High-dose cytosine arabinoside (araC) in the treatment of patients with acute non-lymphocytic leukaemia (ANLL). Blood Abstr 504:191a
9. Piall EM, Aherne GW, Marks VM (1979) A radioimmunoassay for cytosine arabinoside. Br J Cancer 40:548–556
10. Pickup JC, Keen H (1980) Continuous subcutaneous insulin infusion: a developing tool in diabetes research. Diabetologia 18 (1):1–4
11. Rai KR, Glidewell O, Weinberg V, Holland JF (1981) Long-term remission in acute myelocytic leukaemia (AML): Report of a multi-institutional co-operative study. Proc Am Soc Clin 22:481
12. Rees JKH, Sandler RM, Challener J, Hayhoe FCJ (1977) Treatment of acute myeloid leukaemia with a triple cytotoxic regime: DAT. Br J Cancer 36:770–776
13. Slevin ML, Piall EM, Aherne GW, Johnston A, Lister TA (1981) The pharmacokinetics of subcutaneous cytosine arabinoside in patients with acute myelogenous leukaemia. Br J Clin Pharmacol 12:507–510