Cancer Chemother Pharmacol (1989) 23: 373–376

Cancer Chemotherapy and Pharmacology

Treatment of relapsed and refractory acute leukaemia with high-dose cytosine arabinoside and etoposide

Martin Gore, Ray Powles, Anil Lakhani, Sarah Milan, Jennifer Maitland, Glen Goss, Ann Nandi, Timothy Perren, Garry Forgeson, Jennifer Treleaven, Ayed Zuiable, and Fulvio Porta

Leukaemia Unit, Royal Marsden Hospital and Institute of Cancer Research, Sutton, Surrey, U. K

Summary. A total of 65 patients under the age of 55 with acute leukaemia received high-dose cytosine arabinoside (Ara-C) in combination with high-dose etoposide without an anthracycline. Complete remission rates for patients with relapsed or refractory acute myelogenous leukaemia (AML) were 15/25 (60%) and 11/16 (69%), respectively. The complete remission rate for patients with refractory or relapsed acute lymphoblastic leukaemia (ALL) was 10/18 (56%). The treatment-related mortality was 17%. Nine patients whose leukaemia relapsed after matched allogeneic, sibling bone-marrow transplantation (BMT) were also treated in this way; the treatment-related mortality in this group was high (7/9) and the duration of remission in the two patients who responded, too short to justify this intensive treatment in such patients. Similarly, patients who underwent BMT after achieving a complete remission with high-dose Ara-C and etoposide did very poorly, only one patient surviving well and disease-free at 8 months. The important finding in this study was the high complete remission rate rapidly obtained in patients with relapsed or refractory AML without using an anthracycline.

Introduction

Cytosine arabinoside (Ara-C) given in conventional doses to previously untreated patients with acute myelogenous leukaemia (AML) results in a 25% complete remission rate when given as a single agent over 5–7 days [3, 6, 10, 12, 29, 30]. Tumour cells may become resistant to low concentrations of Ara-C, but in vitro studies suggest that some of the proposed mechanisms of resistance can be overcome by exposing the cells to higher concentrations of drug [28]; the dose of Ara-C may need to be 10–100 times greater than that which is effective against Ara-C-sensitive cell lines [8, 9, 20, 21]. In vivo studies of Ara-C toxicity in man have shown that it is possible to obtain these high concentrations safely by the administration of equivalently large doses [11, 27], and such treatment has been shown to be effective against acute leukaemia that is resistant to conventional doses of Ara-C [27].

In the last 5 years a number of groups have used high doses of Ara-C alone and in combination with other drugs to treat relapsed leukaemia or leukaemia that is refractory to conventional therapy [1, 4, 5, 13–15, 19, 23, 26, 31]. The complete remission rates in these studies vary widely and for patients with AML, rates of 25%–70% are reported [15, 23]. In these studies several drugs have been used in combination with high-dose Ara-C: doxorubicin [13], daunorubicin [31], asparaginase [1, 5] mAMSA [15, 16] and mitoxantrone [19]. However, no randomised trials have been done to compare single-agent Ara-C with any of these combinations and no one particular combination appears to be superior.

Etoposide has activity against acute leukaemia when given as a single agent [7], and pre-clinical studies have shown that there is synergism between Ara-C and etoposide [25]. There have been no reports of any large series of patients treated with a combination of etoposide and high-dose Ara-C for AML, although a report has been published in which this combination was used in a small group of 15 patients with acute lymphoblastic leukaemia (ALL) [22]. We present our experience of treating AML and ALL at relapse and when refractory to conventional therapy with high doses of Ara-C in combination with high-dose etoposide.

Materials and methods

Between January 1984 and June 1986, 65 patients at the Royal Marsden Hospital, Sutton, Surrey, received high-dose Ara-C with etoposide for 68 episodes of acute leukaemia (AML or ALL). In all, 38 patients (19 men and 19 women aged 1–47; median age, 29) were treated for 41 episodes of AML, 18 (11 men and 7 women aged 3–52; median age, 24) were treated for ALL, and 9 (6 men and 3 women aged 10–48; median age, 27) were treated for relapsed leukaemia following bone marrow transplantation (BMT).

Patients were entered into the study only if they had either failed conventional leukaemia induction therapy (initial failures) or were in first or subsequent relapse (relapsed patients). All individuals had previously received anthracycline-containing combination chemotherapy. Patients gave fully informed consent as laid down by the Ethics Committee of the Royal Marsden Hospital.

Ara-C was infused i.v. at a dose of 2 g/m^2 over 3 h twice daily for 5 consecutive days, and 100 mg/m^2 etoposide was given i.v. over 1 h either once (etoposide o.d.) or twice (etoposide b.i.d.) daily for 5 days. Patients received one cycle of this treatment. Table 1 shows the treatment

Offprint requests to: Martin Gore

Table 1. Distribution of diagnoses and treatments for episodes of leukaemia treated by high-dose Ara-C + etoposide

	Ara-C + etoposide o.d.	Ara-C + etoposide b.i.d.	Total
AML	35	6	41
ALL	17	1	18
Post-BMT	8	1	9
Total	60	8	68

Table 2. FAB group and disease status of patients with AML

M2	9	Initial failure	16
M3	6	1st relapse	18
M4	13	2nd relapse	6
M5	7	3rd relapse	1
M6	3		

Table 3. Complete remission rate in AML patients treated with high-dose Ara-C + etoposide, once (o.d.) or twice (b.i.d.) daily

	Initial failures (%)	Relapsed patients (%)	Total (%)
Ara-C + etoposide o.d.	67 (10/15)[a]	65 (13/20)[a]	66 (23/35)[a]
Ara-C + etoposide b.i.d.	– (1/1)	40 (2/5)	50 (3/6)
Total	69 (11/16)	60 (15/25)	63 (26/41)

[a] Numbers in parentheses represent the number of remissions /total number of episodes of AML treated

patients received according to diagnosis. The FAB group for patients with AML and their disease status at the time of treatment are shown in Table 2.

All patients received prednisolone eye drops every 2 h for at least 1 week starting on the 1st day of treatment to reduce the incidence of keratitis [24]. In all, 68% of the patients also received systemic steroids to alleviate side effects such as vomiting and vasculitis; they were given 16 mg dexamethasone/day or 20–40 mg prednisolone/day, and treatment usually lasted 1–2 weeks. Prophylactic antiemetics and antidiarrhoeals were also given, including benzodiazepines, phenothiazines, metoclopramide and codeine phosphate.

Results

AML

Table 3 shows the results of high-dose Ara-C with etoposide for the treatment of patients with relapsed (relapsed patients) or refractory AML (initial failures). The complete remission rate in patients who had failed conventional remission induction chemotherapy was 69% (11/16; median acturial duration of remission, 238 days) and 60% (15/25; median actuarial duration of remission, 135 days) in those treated for on episode of relapse.

Deaths other than those due to leukaemia that occurred within 6 weeks of the end of treatment were considered to be treatment-related: there were seven in all; three were initial failure patients and four had relapsed disease. The complete response and treatment-related mortality rates were analysed according to age, sex, FAB classification, disease status, concomitant use of steroids and whether the etoposide was given once or twice a day. None of these parameters affected the complete response rate in particular: it was unaffected by the use of steroids. Similarly, treatment-related mortality was remarkably constant in all groups, 14%–26% (19% overall), except that all of the patients who died were female; however, this was not statistically significant.

ALL

A total of 18 patients were treated with high-dose Ara-C and etoposide for ALL after having either relapsed or failed initial, conventional remission induction chemotherapy. The complete remission rate was 56% (10/18; median actuarial duration, 106 days) with treatment-related mortality of 17% (3/18). There was no difference in the complete remission rate or treatment-related mortality when these were analysed by age, sex, disease status and sub-type. Table 4 shows the distribution of ALL sub-type and the disease status of patients treated with high-dose Ara-C and etoposide.

BMT

Nine patients (seven with AML and two with ALL) who had relapsed following BMT were treated with high-dose Ara-C and etoposide. The results were extremely poor, with seven treatment-related deaths. Two patients achieved complete remissions, but these were only of short duration (3 and 12 months).

Results were also poor for ten patients with AML (six initial failures and four relapsed patients) who achieved complete remissions with high-dose Ara-C and etoposide and then went on to BMT. The median time between the chemotherapy and the transplant was 113 days (range, 42–301 days). Six patients died of transplant-related complications within 6 months of the graft, three relapsed and died within the same period and one is alive and disease-free at 8 months.

Toxicity

Table 5 shows the toxicity of high-dose Ara-C and etoposide given with or without steroids. The nine post-BMT patients do not form part of this analysis. The commonest toxicity was diarrhoea, which occurred in 51% of patients overall; its incidence was greatest in those patients receiving etoposide twice daily ($P < 0.01$). Similarly, intestinal obstruction tended to occur more commonly in this group of patients. The overall incidence of vomiting (WHO grade 3–4) was 19%, but 40% of the patients who did not

Table 4. Distribution of sub-type and disease status in patients with ALL

C-ALL	12	Initial failure	5
T-ALL	1	1st relapse	6
B-ALL	1	2nd relapse	4
N-ALL	3	3rd relapse	2
Not known	1	5th relapse	1

Table 5. Toxicity of high-dose Ara-C + etoposide. Only patients with WHO toxicity grades 3-4 were included in this analysis, except those with a skin rash +, present; −, not present

	Total (%)	+ Steroids (%)	− Steroids (%)	Ara-C + etoposide o.d. (%)	Ara-C + etoposide b.i.d. (%)
Diarrhoea	51 (30/59)[a]	46 (18/39)[a]	60 (12/20)[a]	44 (23/52)[a,b]	100 (7/7)[a,b]
Intestinal obstruction	14 (8/59)	18 (7/39)	5 (1/20)	11 (6/52)	29 (2/7)
Vomiting	19 (11/59)	8 (3/39)[b]	40 (8/20)[b]	21 (11/52)	–
Skin rash	20 (12/59)	23 (9/39)	15 (3/20)	21 (11/52)	14 (1/7)
Pulmonary	7 (4/59)	8 (3/39)	5 (1/20)	8 (4/52)	–
Conjunctivitis	3 (2/59)	3 (1/39)	5 (1/20)	4 (2/52)	–
Headache	3 (2/59)	–	10 (2/20)	4 (2/52)	–
Cerebellar syndrome	2 (1/59)	3 (1/39)	–	2 (1/52)	–
Fits/drowsiness	2 (1/59)	–	5 (1/20)	2 (1/52)	–
Treatment-related deaths	19 (11/59)	18 (7/39)	20 (4/20)	19 (10/52)	14 (1/7)

[a] Numbers in parentheses represent the number of treatments in which toxicity occurred/total number of treatments
[b] Difference statistically significant (see text)

receive steroids had vomiting compared with 8% of the steroid-treated patients ($P < 0.01$). The overall death rate within 6 weeks of finishing chemotherapy was 19% and was very similar for each group of patients. The addition of steroids did not affect the complete remission rate or overall treatment-related mortality.

The median duration of WHO grade 4 neutropenia was 28 days (range, 17–67) for all patients with AML and 24 days (range, 16–33) for those with ALL. There were no significant differences between any of the sub-groups of patients.

Discussion

We showed a complete remission rate of 63% in patients with relapsed or refractory AML treated with a combination of high-dose Ara-C and etoposide. Only two published series show as good a complete remission rate in a similar group of patients [5, 15]. In the former report, Ara-C was used at a dose of 3 g/m^2 every 12 h for 12 doses in combination with mAMSA; in the latter, 3 g/m^2 was given every 12 h for 4 doses together with asparaginase, this combination being repeated after 1 week. Although the remission rate was high in the former study, so was the incidence of serious neurological side effects (cerebellar dysfunction occurred in 7/40 patients, somnolence in 6/40 and mild dysarthria in 8/40). Indeed, it has been shown that the incidence of CNS toxicity rises as the total dose exceeds 24 g/m^2 [17, 18], and it has been suggested that giving 2 g/m^2 Ara-C for 6 days reduces the incidence of CNS toxicity [2, 26]. Our data supports the view that a slightly lower dose of Ara-C results in a low incidence of CNS toxicity without altering the effectiveness of the regimen.

Ara-C with etoposide is a useful treatment for refractory or relapsed acute leukaemia and we recommend its use in these circumstances, as remission rates are high. However, patients require intensive support and treatment-related mortality is not insignificant. Patients who relapse after BMT have high treatment-related mortality; there is a similarly poor outcome for those who go on to BMT after receiving high-dose Ara-C and etoposide. These results therefore call into question the advisability of patients' receiving BMT either before or after treatment with this regimen. Two patients, one with prolymphocytic leukaemia and one with T-cell ALL (data not shown) were treated with high-dose Ara-C and etoposide having relapsed after autologous BMT, and although they both failed to achieve complete remission and eventually died, their deaths were not treatment-related. Similarly, five patients underwent treatment involving autologous BMT after high-dose Ara-C and etoposide, and although all patients died within 6 months of receiving their autograft, only two of the deaths were treatment-related.

Our initial experience would therefore suggest that programmes including autologous bone marrow grafting may be suitable for patients who have previously undergone high-dose Ara-C and that patients who have relapsed after such programmes may be suitable candidates for high-dose Ara-C as salvage therapy. However, there is a need for more data, particularly in view of current schedules for the treatment of AML that include autologous BMT. Higher doses of Ara-C than those in this study or a greater number of courses would probably not increase the complete remission rate but might increase the incidence of side effects and are thus not justified.

Acknowledgements. We thank Pfizer Ltd. for providing the Ara-C and the Leukaemia Research Fund for its support.

References

1. Amadori S, Papa G, Avvisati G, Fenu S, Monarca B, Petti MC, Pulsoni A, Mandelli F (1984) Sequential combination of high dose Ara-C (HIDAC) and asparaginase (ASP) for the treatment of advanced acute leukaemia and lymphoma. Leuk Res 8: 729–734
2. Barnett MJ, Richards MA, Ganesan TS, Waxman JH, Smith BF, Butler MG, Rohatines AZS, Slevin ML, Lister TA (1985) Central nervous system toxicity of high-dose cytosine arabinoside. Semin Oncol 12 (2 Suppl 3): 227–232
3. Bodey GP, Coltman CA, Freireich EJ, Bonnet JD, Gehan EA, Haut AB, Hewlett JS, McCredit KB, Saiki JH, Wilson HE (1974) Chemotherapy of acute leukaemia – comparison of cytarabine alone and in combination with vincristine, prednisolone and cyclophosphamide. Arch Intern Med 133: 260–266
4. Cantin G, Brennan JK (1984) High dose cytosine arabinoside for acute non-lymphocytic leukaemia. Am J Hematol 16: 59–66
5. Capizzi RL, Poole M, Cooper MR, Richards F II, Stuart JJ, Jackson DV Jr, White DR, Spurr CL, Hopkins JO, Muss HB,

Rudnick SA, Wells R, Gabriel D, Ross D (1984) Treatment of poor risk acute leukaemia with sequential high dose Ara-C and asparaginase. Blood 63: 694–700

6. Carey RW, Ribas-Mundo M, Ellison RR, Glidewell O, Lee ST, Cuttner J, Levy RN, Silver R, Blom J, Haurani F, Spurr CL, Harley JB, Kyle R, Moon JH, Eagen RT, Holland JH (1975) Comparative study of cytosine arabinoside therapy alone combined with thioguanine, mercaptopurine or daunorubicin in acute myelocytic leukaemia. Cancer 36: 1560–1566
7. Cavalli F, Sonntag R, Brunner KW (1975) Epipodophyllotoxin VP16-213 in acute non-lymphoblastic leukaemia. Br Med J 4: 227
8. Chu MY, Fischer GA (1965) Comparative studies of leukemic cells sensitive and resistant to cytosine arabinoside. Biochem Pharmacol 14: 333–341
9. Drewinko B, Ho DHW, Barranco SC (1972) The effects of arabinosyl cytosine on cultured human lymphoma cells. Cancer Res 32: 2737–2742
10. Ellison RR, Holland JF, Weil M, Jacquillat C, Boiron M, Bernard J, Sawitsky A, Rosner F, Gussoff B, Silver RT, Karanas A, Cuttner J, Spurr CL, Hayes DM, Blom J, Leone LA, Haurani F, Kyle R, Hutchison JL, Forcier RJ, Moon JH (1968) Arabinosyl cytosine: a useful agent in the treatment of acute leukaemia in adults. Blood 32: 507–523
11. Frei E III, Bicker JN, Hewlett JS, Lane M, Leary WV, Talley RW (1969) Dose schedule and antitumour studies of arabinosyl cytosine (NSC 63878). Cancer Res 29: 1325–1332
12. Gale RP (1979) Advances in the treatment of acute myelogenous leukemia. N Engl Med J 300: 1189–1199
13. Herzig RH, Herzig GP, Lazarus HM, Wolff SN, Phillips GL (1982) High dose cytosine arabinoside in the treatment of refractory acute non-lymphocytic leukaemia in adults: results of two six day regimens. Med Pediatr Oncol [Suppl] 1: 229–233
14. Herzig RH, Wolff SN, Lazarus HM, Phillips GL, Karanes C, Herzig GP (1983) High dose cytosine therapy for refractory leukaemia. Blood 62: 361–369
15. Hines JD, Oken MM, Mazza JJ, Keller AM, Streeter RR, Glick JH (1984) High dose cytosine arabinoside and m-AMSA is effective therapy in relapsed acute non-lymphocytic leukaemia. J Clin Oncol 2: 545–549
16. Hines JD, Mazza JJ, Oken MM, Bennett JM, Adelstein DJ, Keller A, O'Connell MJ (1985) High-dose cytosine arabinoside and mAMSA induction and consolidation in patients with previously untreated de novo acute nonlymphocytic leukaemia: phase I pilot study for the Eastern Cooperative Oncology Group. Semin Oncol 12: (2 Suppl 3): 117–119
17. Hwang TL, Yung WK, Estey EH, Fields WS (1985) Central nervous system toxicity of high-dose Ara-C. Neurology 35 (10): 1475–1479
18. Lazarus HM, Herzig RH, Herzig GP, Phillips GL, Roessmann U, Fishman DJ (1981) Central nervous system toxicity of high dose systemic cytosine arabinoside. Cancer 48: 2577–2582
19. Marcus RE, Catovsky D, Goldman JM, Galton DAG, Newland AC, Slocombe G, Hedge U (1985) Mitozantrone and high dose cytarabine in adult acute myeloid leukaemia. Lancet i: 1384
20. Momparler RL (1974) A model for the chemotherapy of acute leukaemia with 1-B-D-arabinofuranosyl cytosine. Cancer Res 34: 1775–1787
21. Momparler RL, Chu MY, Fisher GA (1968) Studies on a new mechanism of resistance of L5178Y murine leukaemia cells to cytosine arabinoside. Biochim Biophys Acta 161: 481–493
22. Morra E, Lazzarino M, Alessandrino EP, Inverardi D, Canevari A, Bernasconi C (1984) VP16-213 and cytosine arabinoside combination chemotherapy for refractory acute lymphoblastic leukaemia in adults. Eur J Cancer Clin Oncol 20: 1471–1475
23. Preisler HD, Epstein J, Barcos M, Priore R, Raza A, Browman GP, Vogler R, Winton E, Grunwald H, Rai K, Brennan J, Bennett J, Goldberg J, Gottlieb A, Chervenick P, Joyce R, Miller K, Larson R, D'Arrigo P, Doeblin T, Stein M, Bloom M, Steele R, Lee H (1984) Prediction of response of acute nonlymphocytic leukaemia to therapy with "high dose" cytosine arabinoside. Br J Haematol 58: 19–32
24. Ritch P, Hansen R, Heuer D (1983) Ocular toxicity from high-dose cytosine arabinoside. Cancer 51: 430–432
25. Rivera G, Avery T, Roberts D (1975) Response of L1210 to combinations of cytosine arabinoside and VM26 or VP16-213. Eur J Cancer 11: 639–647
26. Rohatiner A, Slevin ML, Dhaliwal HS, Malpas JS, Lister TA (1984) High-dose cytosine arabinoside: response to therapy in acute leukaemia and non-Hodgkin's lymphoma. Cancer Chemother Pharmacol 12: 90–93
27. Rudnick SA, Cadman EC, Capizzi RL, Skeel RT, Bertino JR, McIntosh S (1979) High dose cytosine arabinoside (HDARAC) in refractory acute leukaemia. Cancer 44: 1189–1193
28. Rustum YM, Slocum HK, Wang G, Bakshi D, Kelly E, Buscaglia D, Wrzosek C, Early AP, Preisler H (1982) Relationship between plasma Ara-C and intracellular Ara-CTP pools under conditions of continuous infusion and high dose Ara-C treatment. Med Pediatr Oncol [Suppl] 1: 33–43
29. Southwest Oncology Group (1974) Cytarabine for acute leukaemia in adults: effects of schedule on therapeutic response. Arch Intern Med 133: 251–259
30. Wang JJ, Selawry OS, Vietti TJ, Bodey GP (1970) Prolonged infusion of arabinosyl cytosine in childhood leukaemia. Cancer 25: 1–6
31. Willemze R, Zwaan FE, Colpin G, Keuning JJ (1982) High dose cytosine arabinoside in the management of refractory acute leukaemia. Scand J Haematol 29: 141–146

Received January 28, 1988/Accepted October 1, 1988