Cancer Chemother Pharmacol (1990) 27: 76–78

Cancer Chemotherapy and Pharmacology

Short communication

Cerebellar toxicity during cytarabine therapy associated with renal insufficiency

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Received 1 March 1990/Accepted 2 April 1990

Summary. Acute cerebellar toxicity with ataxia and dysarthria is a well-known side effect during high-dose cytarabine therapy. Dose, age, previous neurological disorders, hepatic dysfunction, and renal insufficiency have been inconsistently reported as risk factors. The present paper presents a patient with renal insufficiency who developed severe cerebellar toxicity following treatment with a dose of cytarabine (8 g/m^2 over 5 days) not generally expected to be associated with neurotoxicity. Together with a review of the literature, the present case gives evidence of renal insufficiency as a major risk factor in the development of cerebellar toxicity during cytarabine therapy. Reduced doses of cytarabine should be considered in patients with renal impairment.

Introduction

Neurotoxicity, a well-known adverse effect following high-dose cytarabine treatment, has been reported in 5%–50% of treatment courses [1, 7, 11, 12, 14, 21]. Several risk factors for the development of neurotoxicity have been described: cumulative dose of cytarabine [2, 14], age [10, 12], past history of neurological dysfunction [16], and hepatic dysfunction [16]. However, none of the reported risk factors have been consistently identified. Not until very recently has renal insufficiency been considered a possible risk factor [7].

This paper presents a patient with renal insufficiency who developed severe acute cerebellar toxicity following treatment with a dose of cytarabine generally not considered to be associated with neurotoxicity.

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Case report

The patient was a 73-year-old man with acute myeloblastic leukaemia, FAB type M2. Induction therapy was initiated with aclarubicin and cytarabine (180 mg daily for 7 days) and induced a partial remission. Another induction course of aclarubicine cytarabine was then given at a dose of 200 mg daily for 7 days. During the subsequent neutropenic period, the patient became febrile and started empiric antibiotic treatment that included tobramycin. A few days later, serum creatinine levels rose abruptly to a maximum of 855 μmol/l. Tobramycin was withheld and haemodialysis was instituted, resulting in steady improvement of renal function.

A follow-up bone marrow examination showed complete remission, and consolidation chemotherapy with high-dose cytarabine therapy was initiated at a dose of 2 g twice daily. On the 1st day of cytarabine therapy, the serum creatinine value was 117 μmol/l, which increased to 316 μmol/l on the following day and fluctuated between 255 and 287 μmol/l over the next 4 days. Comparison of the creatinine and urea levels over a longer period showed it to be very likely that the initial creatinine measurement was spurious. Because of the persistent rise in serum creatinine values, the cytarabine dose was reduced to 1 g twice daily. On the 5th day of treatment after having received 14 g (= 8 g/m^2) cytarabine, the patient developed severe ataxia (unable to ambulate) and severe dysarthria (incomprehensible speech). He remained conscious but showed personality changes with aggressive traits. The cytarabine infusion was discontinued.

The neurological symptoms persisted unchanged for almost 2 weeks. On the 12th day the patient experienced a temperature rise to 41.7°C accompanied by signs of septic shock and received an intravenous dose of 100 mg prednisolone. The following day his speech was almost restored to normal, and he showed fast improvement in walking function and could walk alone 1 week later. The patient was discharged 19 days after the first appearance of neurotoxic symptoms. During continued prednisolone treatment of 50 mg daily, he demonstrated complete neurological restoration after 1 month. The prednisolone dose was gradually tapered after 2 months without problems. The patient had no prior neurological disorders. His hepatic function and platelet count were within the normal ranges at the time of onset of the neurological symptoms.

Discussion

Cytarabine has been recognized as an important drug in the treatment of acute leukaemia over the last two decades [9]. Improvement in remission rates, especially in refractory

acute leukaemia, was reported after the introduction of high-dose cytarabine in 1979 [17]. In an attempt to increase the remission rates further even higher doses were used, and a new side effect of severe and in some cases fatal cerebellar toxicity was observed [14]. The clinical picture was dominated by the cerebellar dysfunction with dysarthria, dysdiadochokinesia, and ataxia. Cerebral dysfunction with personality changes, seizures, somnolence, or coma also occurred [14]. Autopsy studies have revealed gliosis and considerable degeneration and decrease in the number of Purkinje cells in the cerebellar hemispheres and the vermis [1, 3, 8, 11, 18, 21].

Cerebellar function is in most cases restored to normal within 10 days, but dysfunction may persist for several months and is occasionally irreversible [1, 6, 12, 14, 16, 21]. No specific therapy is known. Because of concurrent septic shock, the present patient received 100 mg prednisolone and subsequently showed a prompt improvement in cerebellar function. The sudden improvement after prednisolone might be a mere coincidence, but it could also indicate a possible beneficial effect of prednisolone in cytarabine-induced neurotoxicity.

After intravenous infusion, cytarabine is rapidly inactivated (mainly in the liver) by cytidine deaminase to arabinosyl uracil (ara-U), a relatively nontoxic compound [4]. Within the normal therapeutic dose range, cytidine deaminase does not seem to become saturated [19]. After a single injection, 80% of the drug is excreted in the urine within 24 h, mostly as ara-U [13]. Shortly after an intravenous injection, the concentration of cytarabine in cerebrospinal fluid is 60% of that in plasma [13]. After several hours, the level in cerebrospinal fluid exceeds that in plasma because of the low concentration of cytidine deaminase in the brain parenchyma [5, 13, 19, 20].

In the earliest report [14] the neurotoxicity was found to be dose-related, with no CNS dysfunction occurring below a critical total dose of 36 g/m^2; it was concluded that doses of <54 g/m^2 resulted in only minimal side-effects. However, a subsequent study [8] found a high frequency of neurotoxicity among elderly patients, even at doses as low as 18 g/m^2. The age-dependent risk of neurotoxicity was confirmed in a later study [12], and reduced doses of cytarabine were recommended in patients of >50 years of age [12].

In previous reports of cytarabine and neurotoxicity, renal insufficiency was not considered to be a risk factor, and data on renal function in patients who developed neurotoxicity have not been presented. In 1987, Herzig et al. [12] noted that several patients with cerebellar toxicity either had or developed renal insufficiency; no supportive data for this possible association were given. In the paper published by Damon et al. in 1989 [7], it was found that 16 of 26 (62%) courses of high-dose cytarabine in patients with renal insufficiency were complicated by neurotoxicity, as opposed to only 10 of 121 (8%) in the group with normal renal function. No dose-dependent risk of neurotoxicity was found [7].

Ara-U is eliminated by renal excretion and has a half-life in plasma of about 4 h. In vitro, it exerts an inhibitory effect on cytidine deaminase activity [5]. In renal impairment, the level of ara-U in plasma rises, which might inhibit cytidine deaminase and consequently increase the cytarabine concentration, thereby augmenting the risk of neurotoxic side effects.

Moderate neurotoxicity has been reported after a dose of 12 g/m^2 [16]. To the author's knowledge, only one patient has thus far been reported to show signs of severe cerebellar toxicity following a total cytarabine dose of <10 g/m^2. A patient with large-cell carcinoma of the lung who received cisplatin and two courses of 3 g/m^2 cytarabine developed renal impairment and cerebellar toxicity. Plasma and cerebrospinal fluid concentrations of ara-U were found to be much higher and more sustained than those recorded during treatment courses given under conditions of normal renal function [15]. The present case adds further support to the suggestion that renal insufficiency is a major risk factor in the development of cerebellar toxicity during cytarabine therapy. Reduced doses of cytarabine should be considered in patients with renal impairment.

References

1. Barnett MJ, Richards MA, Ganesan TS, Waxman JH, Smith BF, Butler MG, Rohatiner AZS, Slevin ML, Lister TA (1985) Central nervous system toxicity of high-dose cytosine arabinoside. Semin Oncol 12 [Suppl 3]: 277
2. Benger A, Browman GP, Walker IR (1985) Clinical evidence of a cumulative effect of high-dose cytarabine on the cerebellum in patients with acute leukemia. Cancer Treat Rep 69: 240
3. Boesen P, Fallingborg J, Spaun E (1988) Severe persistent cerebellar dysfunction complicating cytosine arabinoside therapy. Acta Med Scand 224: 189
4. Camiener GW, Smith CG (1965) Studies of the enzymatic deamination of cytosine arabinoside – part I. Biochem Pharmacol 14: 1405
5. Capizzi RL, Yang JL, Cheng E, Bjornsson T, Sahasrabudhe D, Tan R-S, Cheng Y-C (1983) Alteration of the pharmacokinetics of high-dose ara-C by its metabolite, high ara-U, in patients with acute leukemia. J Clin Oncol 1: 763
6. Cold S (1986) Cerebellar dysfunction during high-dose cytosine arabinoside therapy in a case of acute myelogenous leukaemia. Scand J Haematol 36: 165
7. Damon LE, Mass R, Linker CA (1989) The association between high-dose cytarabine neurotoxicity and renal insufficiency. J Clin Oncol 7: 1563
8. Dworkin LA, Goldman RD, Zivin LS, Fuchs PC (1985) Cerebellar toxicity following high-dose cytosine arabinoside. J Clin Oncol 3: 613
9. 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 FJ, Moon JH (1968) Arabinosyl cytosine: a useful agent in the treatment of acute leukemia in adults. Blood 32: 507
10. Gottlieb D, Bradstock K, Koutts J, Robertson T, Lee C, Castaldi P (1987) The neurotoxicity of high-dose cytosine arabinoside is age related. Cancer 60: 1439
11. Grossman L, Baker MA, Sutton DMC, Deck JHN (1983) Central nervous system toxicity of high-dose cytosine arabinoside. Med Pediatr Oncol 11: 246
12. Herzig RH, Hines JD, Herzig GP, Wolff SN, Cassileth PA, Lazarus HM, Adelstein DJ, Brown RA, Coccia PF, Strandjord S, Mazza JJ, Fay J, Phillips GL (1987) Cerebellar toxicity with high-dose cytosine arabinoside. J Clin Oncol 5: 927
13. Ho DHW (1977) Potential advances in the clinical use of arabinosyl cytosine. Cancer Treat Rep 61: 717

14. 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
15. Lopez JA, Agarwal RP (1984) Acute cerebellar toxicity after high-dose cytarabine associated with CNS accumulation of its metabolite, uracil arabinoside. Cancer Treat Rep 68: 1309
16. Nand S, Messmore HL, Patel R, Fisher SG, Fisher RI (1986) Neurotoxicity associated with systemic high-dose cytosine arabinoside. J Clin Oncol 4: 571
17. Rudnick SA, Cadman EC, Capizzi RL, Skeel RT, Bertino JR, McIntosh S (1979) High dose cytosine arabinoside (HDARAC) in refractory acute leukemia. Cancer 44: 1189
18. Salinsky MC, Levine RL, Aubuchon JP, Schutta HS (1983) Acute cerebellar dysfunction with high-dose ara-C therapy. Cancer 51: 426
19. Slevin ML, Piall EM, Aherne GW, Harvey VJ, Johnston A, Lister TA (1983) Effect of dose and schedule on pharmacokinetics of high-dose cytosine arabinoside in plasma and cerebrospinal fluid. J Clin Oncol 1: 546
20. Spector R (1982) Pharmacokinetics and metabolism of cytosine arabinoside in the central nervous system. J Pharmacol Exp Ther 222: 1
21. Winkelman MD, Hines JD (1983) Cerebellar degeneration caused by high-dose cytosine arabinoside: a clinicopathological study. Ann Neurol 14: 520