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Arsenic in the cerebrospinal fluid of a patient receiving arsenic trioxide for relapsed acute promyelocytic leukemia with CNS involvement

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Abstract

We report on a 42-year-old patient whose relapse of acute promyelocytic leukaemia (APL) included meningeal infiltration. Since he had previously experienced ATRA syndrome, he received arsenic trioxide (ATO) plus intrathecal therapy with cytarabine, prednisone and methotrexate. We measured the concentration of arsenic in his cerebrospinal fluid (CSF). Arsenic showed a peak CSF concentration of 0.008 mg/l (0.11 µmol/l)) and a nadir of 0.002 mg/l (0.027 µmol/l), both representing about 14% of blood levels. ATO thus crosses the blood-CSF-barrier when administered intravenously, but the concentration in CSF is probably not sufficient for treatment of meningeal leukemia.

Keywords: arsenic; arsenic trioxide; cerebrospinal fluid; blood-cerebrospinal fluid-barrier; acute promyelocytic leukemia

Introduction

Arsenic trioxide (ATO) is an effective treatment for relapsed and newly diagnosed acute promyelocytic leukaemia (APL) [1,2]. It has an apoptotic effect on APL cells, probably attributable to downregulation of bcl-2 expression at both mRNA and protein levels, as well as degration of PML-RARα, the abnormal fusion protein in APL. Antiangiogenic mechanisms are also discussed [3, 4, 5, 6]. Even as a single agent, ATO is sufficiently active to induce PCR-negative complete remissions (CR) [7]. Side effects mainly involve dermatological and gastrointestinal symptoms [4] which usually do not lead to discontinuation of treatment. Plasma pharmacokinetics show a peak of 4.2 to 6.7 μmol/l [3] 3-4 hours after infusion. Continuous treatment for weeks did not alter plasma concentrations of arsenic [4]. No data are available on CSF concentrations. Therefore, it is as yet unknown whether ATO crosses the blood-CSF-barrier and may thus be active against meningeal infiltration.

Case report

APL with a typical PML-RARα positive karyotype (46,XY,t(15;17)(q22;q21)[12]) was diagnosed in a 41-year-old male. The patient received chemotherapy (idarubicine and cytarabine) plus all-trans retinoic acid (ATRA) and achieved complete remission. However, ATRA had to be discontinued after 16 days of treatment because of ATRA syndrome with rash and pulmonary oedema. ATRA syndrome responded only partially to corticosteroids. A second cycle of induction therapy included idarubicin, cytarabine, and etoposide. For consolidation, high-dose cytarabine and mitoxantrone were given. A second cycle of consolidation therapy was performed 5 months after the diagnosis. Molecular monitoring for PML-RARα was negative when treatment was completed.

Nevertheless, relapse occurred one year after diagnosis. The karyotype was 46,XY,t(15;17)(q22;q21)[18] / 46,XY,t(1;15;17)(q21;q21q22;q21)[4]. In addition to cyto-

reductive treatment with cytarabine for 6 days, the patient received ATO for 30 days, achieving complete remission again. Relapse treatment also included re-exposure to ATRA, which had to be discontinued after 7 days because of ATRA syndrome with pleural effusions. Again, ATRA syndrom responded only partially to corticosteroids. As consolidation treatment, ATO was administered for 3 weeks, followed by autologous stem cell transplantation (SCT) after conditioning with busulfan and melphalan.

Four months after autologous SCT the patient developed CNS relapse, causing headaches and a seizure. Leukemic blasts in the cerebrospinal fluid showed the typical translocation t(15;17)(q22;q21)[11]). Bone marrow biopsy confirmed relapse of APL with 10% blasts. While conventional cytogenetics found only normal mitoses, FISH revealed that one of 261 cells examined carried a t(15;17). The patient was given ATO 10 mg daily for 30 days plus intrathecal therapy (40mg cytarabine, 40 mg prednisone, and 15mg methotrexate) 3 times weekly for a total of 9 treatments. The neuroaxis was irradiated with 30 Gy.

ATO concentrations were measured in whole blood, serum, and CSF three hours after ATO infusion to assess peak values. Trough levels were measured after 24 hours (prior to the next ATO infusion). Results are given in table 1.

The patient achieved a third complete remission with negative results on molecular monitoring of t(15;17) in blood and CSF. Subsequently, allogeneic stem cell transplantation was performed using a reduced intensity conditioning regimen with fludarabin and total body irradiation. At the time of this writing, the patient is still in complete remission three years after allogeneic transplantation.

Discussion

We have shown that systemic intravenous treatment with ATO leads to detectable levels of ATO in the cerebrospinal fluid. In our patient, ATO concentrations in the CSF were about 12-

16% compared with those in whole blood or serum. Therefore, ATO seems to be capable of crossing the blood-CSF barrier in humans. However, it is unclear to what extent impairment of the barrier through irradiation and/or previous meningeal infiltration helped ATO to permeate the CSF. There was apparently no active meningeal leukemia when the second specimen was taken, since blast clearance had already been achieved in the CSF at that time.

In animals, arsenic given intravenously was detectable in the choroid plexus at concentrations higher than in blood and up to 40-fold higher than in CSF. Accumulation in the choroid plexus may be a mechanism to reduce ATO concentrations in the CSF [8, 9, 10].

In vitro, ATO at a concentration of 0.25 μmol/l did not significantly inhibit the growth of a PML cell line until day 4 [3]. At 0.1 μmol/l, neither growth nor survival of APL cells was altered for 10 days [5]. The latter concentration corresponds to the peak level of arsenic in the CSF of our patient. Therefore, ATO concentrations in CSF achieved by i.v. infusion of the drug are probably insufficient for single agent treatment of meningeal leukemia. As yet, it is unknown whether ATO can be safely administered intrathecally.

Table 1

Material	Nadir (mg/l)/(μmol/l) (day 5 of arsenic treatment)	Peak (mg/l) /(μmol/l) (day 15 of arsenic treatment)
Blood	0.012/0.16	0.065/0.87
Serum	0.016/0.21	
CSF	0.002/0.027	0.008/0.11

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