Cytarabine-induced fever complicating the clinical course of leukemia

Can Gonen[a], Ismail Celik[b], Yesim S. Cetinkaya[c] and Ibrahim Haznedaroglu[d]

The aim of this study is to assess the frequency and clinical characteristics of cytosine arabinoside-induced fever in patients with acute myeloid leukemia in remission, receiving high-dose (3 g/m^2) consolidation therapy. We have investigated 77 consolidation cycles over a study period of 4 years. A strict definition of cytosine arabinoside-induced fever (i.e. patients without neutropenia and with negative blood cultures during the fever episodes) was used. Of the 77 consolidation cycles, fever due to cytarabine was detected in 33 cycles (43%). Median time of onset of fever from the beginning of first chemotherapy dose was 22 h and maximum temperature was in the range 38.0–39.7°C (mean ± SD: 38.8 ± 0.5°C). Median duration of fever was 10.15 h and did not exceed 72 h. There was no difference with regard to neutrophil and white blood cell counts between cycles with or without cytarabine fever. The cost of investigation of fever source was about US$2137. Our analysis suggests that 'cytarabine fever' is a frequent and often a self-limiting complication of high-dose cytosine arabinoside consolidation therapy, and cost-reductive approaches could be structured based on this background. *Anti-Cancer Drugs* 16:59–62 © 2005 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2005, **16**:59–62

Keywords: cytosine arabinoside, fever, leukemia

Departments of [a]Internal Medicine, [b]Medical Oncology, [c]Infectious Diseases and [d]Hematology, Hacettepe University School of Medicine, Ankara, Turkey.

Correspondence to C. Gonen, Dokuz Eylül Sitesi, Ilica Mahallesi, Tur Sokak, No. 8/13, Narlidere, 35320, Izmir, Turkey.
Tel: +90 232 2387777; fax: +90 232 2590541;
e-mail: drcgnn@yahoo.com

Received 13 July 2004 **Revised form accepted** 2 September 2004

Introduction

'Drug-induced fever' refers to a clinical disorder characterized by fever associated with the administration of a drug and disappearing following its discontinuation, when no other cause for the fever is evident after a detailed clinical search [1]. Drug-associated fever has been estimated to occur in approximately 10% of in-patients, and could be a cause of unnecessary testing and prolonged hospitalization [2]. Antineoplastic drugs are responsible for a substantial number of drug-induced fever episodes [3].

The nucleoside analog, cytosine arabinoside (cytarabine/Ara-C), is an effective agent in the treatment of acute myeloid leukemia (AML) [4]. Its active metabolite cytosine arabinoside triphosphate (Ara-CTP) inhibits DNA polymerase by competing with the binding of the natural substrate, deoxycytidine triphosphate. Also, Ara-CTP incorporates into DNA and interferes with DNA synthesis. In addition to direct cytotoxic effects, Ara-C induces perturbations in the expression of various oncogenes as well as lipid second messengers. All these molecules play a role in the programmed cell death [5]. High-dose Ara-C (HDARA-C) regimen (1–3 g/m^2) are widely employed to overcome cellular drug resistance and achieve therapeutic drug levels. Currently, the HDARA-C regimen constitutes a 'standard care' for most AML patients during the post-remission phase [6]. On the other hand, HDARA-C consolidation regimen have substantial toxicities such as myelosuppression, cerebellar dysfunction, skin desquamation, conjunctivitis, hepatotoxicity, pulmonary toxicity and fever [7–9]. There is a paucity of data regarding the characteristics of Ara-C fever with a variable fever incidence in different studies [10,11]. We aimed to analyze our experience with regard to the characteristics of fever due to HDARA-C consolidation regimen in AML patients.

Patients and methods

Hospital records of 162 adult AML patients who were treated between January 2000 and January 2004 were retrospectively reviewed through the use of a comprehensive institutional database of medical diagnosis and procedures. Patients in complete remission after the induction chemotherapy who had received the HDARA-C consolidation regimen were identified. Then, the search was narrowed to those without proven infections and fever at the beginning of the consolidation treatment. We have examined 77 HDARA-C consolidation cycles in 38 eligible AML patients by using the written and computerized medical records together with the pharmacy charts.

Patients receiving consolidation chemotherapy at our institution have been treated in standard rooms without any special ventilation system. Standard precautions were

0959-4973

followed unless there was an indication for another type of isolation (e.g. contact precautions, droplet precautions or airborne precautions). Routine gut decontamination or other prophylactic antibiotics were not used. Pre-consolidation evaluation of the patients consisted of physical examination, routine complete blood count, biochemistry studies, chest X-ray and bone marrow examination. Body temperature measurements were done every 2 h throughout the hospital stay in patients without fever and the interval between two measurements was narrowed according to the patients' status when needed. Complete blood counts were repeated daily in all patients from the admission. The HDARA-C regimen consisted of Ara-C 3 g/m^2 every 12 h on days 1, 3 and 5. Ara-C dosage was reduced to one-third in patients with severe co-morbid disease and patients over the age of 60.

Ara-C fever was defined as a single axillary temperature of 38.3°C (101°F) and above or a temperature of 38.0°C (100.4°F) and above for ≥ 1 h in a patient with a neutrophil count above 500 cells/mm^3 and without an apparent source of fever except Ara-C. Additionally, blood cultures during the fever had to be all negative. Patients who had fever before the beginning of consolidation treatment, taking antimicrobials (even prophylactically) and drugs with high potential for fever (except those related to the leukemia treatment, like allopurinol) or those with proven infections (including fungal infections under control) were excluded from the study.

The relevant data about the characteristics of patients and fever episodes related to HDARA-C administration were collected. An independent samples *t*-test was used with regard to white blood cell and neutrophil counts for the comparison of consolidation cycles with or without Ara-C fever. For the comparison of patients with or without Ara-C fever with regard to gender and additional drug usage (for co-morbid diseases) in the first recorded consolidation cycle, the χ^2-test was used. $p < 0.05$ was considered as statistically significant. SPSS, version 10.0 for Windows, was used to analyze the data.

Results

AML patient characteristics are depicted in Table 1. Twenty-three out of 36 patients (64%) developed fever in at least one of the consolidation cycles. Of the 77 consolidation cycles analyzed in 36 AML patients, fever due to HDARA-C was identified in 33 cycles (43%). The maximum temperature ranged between 38.0 and 39.7°C (mean ± SD: 38.8 ± 0.5°C) and the median time of onset of fever from the beginning of the first chemotherapy dose was 22 h (range 9.20–87.30 h). In eight consolidation cycles, fever initiated in the chemotherapy-free days. In five of these eight cycles, fever was identified on the second day (between 24 and 48 h) and in the remaining three cycles on the fourth day (between 72 and 96 h).

Table 1 Clinical characteristics of the study group

Age (years) [mean (range)]	46.6 ± 15.6 (19–78)
Gender	
male	25 (69%)
female	11 (31%)
AML class (French–American–British)	
M0	1
M1	8
M2	11
M4	10
M5	3
M6	1
Biphenotypic	2

Table 2 Main characteristics of HDARA-C fever

Total no. patients	36
Total consolidation cycles evaluated	77
No. patients who developed fever in at least one consolidation cycle	23 (64%)
No. consolidation cycles in which Ara-C fever detected	33 (43%)
Onset of Ara-C fever from the beginning of chemotherapy (h)	
median (interquartile range)	22 (46, 10)
range	9.2–87.3
Maximum temperature (°C)	
mean ± SD	38.8 ± 0.5
range	38.0–39.7
no. consolidation cycles in which fever 38.0–39.0°C encountered	18
no. consolidation cycles in which fever 39.1–40.0°C encountered	15
Duration of fever (h)	
median (interquartile range)	10.15 (20, 07)
range	1–72

Fever was developed in the first 24 h in 18 out of the 77 consolidation cycles (23%). The median duration of fever was 10.15 h (range 1–72 h). There were fever-free episodes between fever spikes in 11 consolidation cycles. The main characteristics of HDARA-C induced fever are reviewed in Table 2.

The cytarabine scheme was continued in all patients despite fever. Two patients were severely ill with accompanying hypotension and rigors. Acral erythema was observed in one patient. The consolidation scheme was stopped early in two patients because of the cerebellar toxicity of the drug. All blood cultures taken during the fever episodes were negative. Ara-C dose was reduced to 1 g/m^2 (one-third of the usual dose) in six patients because of age (over 60 years) and co-morbid diseases.

White blood cell ($7061.18 \pm 2735.82 \times 10^6$/l) and neutrophil counts ($4952.85 \pm 2359.92 \times 10^6$/l) in consolidation cycles in which Ara-C fever was detected were not different from those in which Ara-C fever was not encountered (6406.98 ± 2537.75 and $4500.93 \pm 2451.56 \times 10^6$/l, respectively). Moreover, there was no difference with regard to gender when the first recorded consolidation cycle was compared between patients with (female/male: 6/8) or without (female/male: 5/17) Ara-C

fever. Drugs taken by the patients other than the HDARA-C were prophylactic glucocorticoid eye drops, standard anti-emetics and drugs related to the additional medical problems. There was no difference with regard to fever between patients using one or more of these additional drugs from patients not using the aforementioned drugs.

For investigation of fever source; a total of 26 blood cultures [unit price (UP): US$43], 21 urine cultures (UP: US$36), six chest X-rays (UP: US$5.8), two sinus X-rays (UP: US$4.9), two oral smears (UP: US$14.2), 11 sterile urine examinations (UP: US$14.2) and six urinalysis (UP: US$5.7) were performed in 33 consolidation cycles with fever. The total cost of these investigations was about US$2137.

Discussion

In this retrospective descriptive study, characteristics of fever due to HDARA-C were analyzed during the consolidation period in patients with AML in complete remission. Fever due to Ara-C is a frequently encountered toxicity of the HDARA-C consolidation protocol (43%) despite the use of strict inclusion criteria in our study. Elucidation of the true incidence of 'Ara-C fever' in everyday clinical practice is very difficult since many chemotherapeutic regimens include drugs other than Ara-C. Moreover, drug usage related to co-morbid diseases makes evaluation of drug fever rather difficult. Ara-C fever was previously reported in 34% of refractory leukemia patients in a toxicity study [10]. In another study, a frequency of 24% was reported in 17 extensively pre-treated patients with relapsed non-Hodgkin's lymphoma [11]. Primary hematologic diseases were not under control in both of these studies. In a pediatric study, fever was encountered in 13 out of 16 patients receiving 2 g/m^2 Ara-C [12]. In our single-agent study, 64% of patients experienced fever in at least one of the consolidation cycles. Fortunately, the toxicity was quite limited and fever never exceed 40°C (Table 2). According to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0, fever of 38°C and above is classified as grade 2 and hypotension accompanying fever as grade 3 (http://ctep.cancer.gov/reporting/ctc.html; last searched at 13 June 2004). All but two patients in our study fulfilled grade 2 toxicity criteria. These two patients had hypotension and rigors accompanying fever. Both of them had been managed conservatively with fluid administration and antipyretics. The consolidation scheme has been continued despite the fever in all patients.

Although drug fever is commonly cited as a cause of fever, this condition has not been extensively reported in the literature [3,13]. The mean lag time between the initiation of an offending agent and the onset of fever changed considerably when a wide variety of drugs responsible for the fever were surveyed [1]. However, fever induced by antineoplastic agents had a significantly shorter median lag time than that associated with any other drug category [1,3]. Our results further supported this observation with a median lag time of 22 h. Ek *et al.* previously reported a median lag time of 28 h in pediatric patients receiving HDARA-C [12]. Approximately 23% of fever episodes were observed in the first 24 h in our study. The maximum duration of fever was 3 days, yet individual fluctuations have been observed.

Ara-C infusions can induce a syndrome consisting of fever, myalgia, abdominal pain, malaise and rash [14]. This 'cytarabine syndrome' has previously been attributed to hypersensitivity or vasculitis, but recent evidence emphasizes the importance of cytokine network activation as the critical initiating pathophysiological trigger [12]. It is proposed that NFκB activation by several pathways in response to Ara-C mediates the production of pro-inflammatory cytokines [12]. Steroids can inhibit activation of NFκB [15] and corticosteroid administration before Ara-C may prevent drug fever [16]. However, this treatment modality needs to be better evaluated in prospective randomized studies. Fever, but not the classical 'cytarabine syndrome', is quite frequent among the AML patients based on our data.

The investigation of fever source associated with HDARA-C cost about US$2137 in 33 Ara-C fever episodes according to our results. This outcome could be due to the paucity of the data regarding the characteristics of Ara-C fever. The lack of local institutional and universal guidelines delineating which laboratory tests and examinations should be done in a febrile patient receiving HDARA-C without neutropenia is also evident. Likewise, the data regarding 'when to do' and 'how much to do' issues is also not available in the current literature. Therefore, our study determining the main characteristics of Ara-C fever might help to constitute a background for future algorithm-creation studies and guidelines about these critical issues. Irrelevant testing can cause patient discomfort, complications and high economic cost—greatly contrasting with the current 'best care' strategy. Moreover, 'the price' could be higher than observed in our study within distinct parts of the world, particularly in Western countries where skilled medical care is far more expensive.

In conclusion, fever due to HDARA-C is a frequent and usually self-limiting adverse effect in AML patients. Median lag time from the initiation chemotherapy to the beginning of fever is short and the duration of fever is not more than 72 h. High-grade fevers (40°C or above) and other toxic manifestations are not common. Irrelevant testing for fever can cause substantial cost. Further

prospective randomized trials are needed to constitute cost-reductive algorithms and to form guidelines for managing this complicated clinical state.

References

1 Mackowiak PA. Drug fever: mechanisms, maxims and misconceptions. *Am J Med Sci* 1987; **294**:275–286.

2 Johnson DH, Cunha BA. Drug fever. *Infect Dis Clin North Am* 1996; **10**: 85–91.

3 Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. *Ann Intern Med* 1987; **106**: 728–733.

4 Mastrianni DM, Tung NM, Tenen DG. Acute myelogenous leukemia: current treatment and future directions. *Am J Med* 1992; **92**:286–295.

5 Grant S. Ara-C: cellular and molecular pharmacology. *Adv Cancer Res* 1998; **72**:197–233.

6 Löwenberg B, Downing JR, Burnett A. Acute myeloid leukemia. *N Engl J Med* 1999; **341**:1051–1062.

7 DeLap RJ. Antimetabolic agents: cytarabine. In: Kirkwood JM, Lotze MT, Yasko JM (editors): *Current Cancer Therapeutics*, 2nd edn. Philadelphia, PA: Current Medicine; 1996, p. 56.

8 Graves T, Hooks MA. Drug-induced toxicities associated with high-dose cytosine arabinoside infusions. *Pharmacotherapy* 1989; **9**:23–28.

9 Altundag O, Altundag K, Celik I, Turker A, Kars A. Isolated hyperbilirubinemia following standard dose cytosine arabinoside in a patient with relapsed acute myeloid leukemia. *Am J Hematol* 2004; **75**:263–264.

10 Kantarjian HM, Estey EH, Plunkett W, Keating MJ, Walters RS, Iacoboni S, *et al.* Phase I–II clinical and pharmacologic studies of high-dose cytosine arabinoside in refractory leukemia. *Am J Med* 1986; **81**:387–394.

11 Shipp MA, Takvorian RC, Canellos GP. High-dose cytosine arabinoside. Active agent in treatment of non-Hodgkin's lymphoma. *Am J Med* 1984; **77**:845–850.

12 Ek T, Jarfelt M, Mellander L, Abrahamsson J. Proinflammatory cytokines mediate the systemic inflammatory response associated with high-dose cytarabine treatment in children. *Med Pediatr Oncol* 2001; **37**:459–464.

13 Marik PE. Fever in the ICU. *Chest* 2000; **117**:855–869.

14 Castleberry RP, Crist WM, Holbrook T, Malluh A, Gaddy D. The cytosine arabinoside (Ara-C) syndrome. *Med Pediatr Oncol* 1981; **9**:257–264.

15 Scheinman RI, Cogswell PC, Lofquist AK, Baldwin Jr AS. Role of transcriptional activation of I kappa B alpha in mediation of immunosuppression by glucocorticoids. *Science* 1995; **270**: 283–286.

16 Chng WJ. Cytarabine syndrome revisited. *Br J Haematol* 2003; **122**:875.