Close Correlation of 1-\(\beta\)-D-Arabinofuranosylcytosine 5'-Triphosphate, an Intracellular Active Metabolite, to the Therapeutic Efficacy of \(N^4\)-Behenoyl-1-\(\beta\)-D-arabinofuranosylcytosine Therapy for Acute Myelogenous Leukemia

Takahiro Yamauchi,\(^1,3\) Yasukazu Kawai,\(^1\) Nobuyuki Goto,\(^2\) Shinji Kishi,\(^1\) Shin Imamura,\(^1\) Akira Yoshida,\(^1\) Yoshimasa Urasaki,\(^1\) Toshihiro Fukushima,\(^1\) Hiromichi Iwasaki,\(^1\) Hiroshi Tsutani,\(^1\) Mikio Masada\(^2\) and Takanori Ueda\(^1\)

\(^1\)First Department of Internal Medicine, and \(^2\)Department of Hospital Pharmacy, Fukui Medical University, 23, Shimoaizuki, Matsuoka, Fukui, 910-1193, Japan

Key words: BHAC, ara-C, ara-CTP, Clinical pharmacokinetics, AUC,

Running title: ara-CTP during BHAC Therapy.

\(^3\)To whom correspondence should be addressed:

E-mail: tyamauch@wt.net
Summary

$N^4$-Behenoyl-1-β-D-arabinofuranosylcytosine (BHAC), a prodrug of 1-β-D-arabinofuranosylcytosine, is used effectively for the treatment of leukemia in Japan. BHAC therapy may be more effective if it is directed by 1-β-D-arabinofuranosylcytosine 5'-triphosphate (ara-CTP), the intracellular active metabolite of ara-C derived from BHAC. However, previous monitoring methods for ara-CTP were less sensitive. Here, using our new sensitive method, we evaluated the ara-CTP pharmacokinetics viewing from the therapeutic response in 11 acute myelogenous leukemia patients who received a 2-h infusion of BHAC (70 mg/m$^2$) in the combination remission induction therapy. ara-CTP at low levels under 1 μM could be monitored. BHAC kept both the plasma ara-C and the intracellular ara-CTP for a longer time, even compared with the historical values of high-dose ara-C. The area under the concentration-time curve of ara-CTP was significantly greater in the patients with complete remission than in the patients without the response. This greater amount of ara-CTP was attributed to the higher ara-CTP concentrations achieved in the responding patients. There was no difference of the plasma ara-C pharmacokinetics between the two groups. Thus, for the first time in BHAC therapy, the ara-CTP pharmacokinetics was evaluated in relation to the therapeutic effect, and the importance of ara-CTP was clinically shown. The optimal BHAC therapy may be directed by the ara-CTP pharmacokinetics in each individual patient.
INTRODUCTION

1-β-D-Arabinofuranosylcytosine (ara-C) is one of the most effective anticancer agents in the treatment of leukemia.\textsuperscript{1-3} The administration of ara-C at a conventional dose in combination with other antileukemic drugs has markedly improved remission rates of the induction therapy for acute myelogenous leukemia (AML).\textsuperscript{1-3} As the mechanism of action, after being transported into leukemic cells, ara-C is phosphorylated to 1-β-D-arabinofuranosylcytosine 5'-monophosphate and then to its active metabolite, 1-β-D-arabinofuranosylcytosine 5'-triphosphate (ara-CTP).\textsuperscript{4} ara-CTP inhibits DNA polymerases in competition with deoxycytidine 5'-triphosphate.\textsuperscript{5-7} A small portion of ara-CTP is incorporated into the DNA strand and terminates the DNA elongation.\textsuperscript{8} Consequently, ara-C exerts its cytotoxic effect by inhibiting DNA synthesis. Therefore, the intracellular ara-CTP is a key metabolite for the mechanism of action,\textsuperscript{5-8} and the cytotoxicity of ara-C is S phase-specific and time-dependent.\textsuperscript{9}

While the cytotoxic effect of ara-C is time-dependent, the drug is rapidly inactivated to 1-β-D-arabinofuranosyuracil by cytidine deaminase in the plasma.\textsuperscript{4, 10} To overcome this dilemma, several derivatives of ara-C, which are long-acting or deaminase-resistant, has been evaluated.\textsuperscript{11-14} N\textsuperscript{4}-Behenoyl-1-β-D-arabinofuranosylcytosine (BHAC) is one of the acyl derivatives of ara-C, which has a long-chain fatty acyl group at the 4-amino position of ara-C,\textsuperscript{11, 12} and thereby is resistant to inactivation by cytidine deaminase.\textsuperscript{12} BHAC was proved to exhibit its cytotoxicity on various experimental tumors regardless of the treatment schedules, mainly because of its resistance to deamination.\textsuperscript{11, 12} Clinically, for over 15 years in Japan, BHAC has been used
effectively in the combination remission induction therapy for AML patients, and provided over 70% remission rates.\textsuperscript{15-17}

The mechanism of action in BHAC is thought to be substantially the same as is seen in ara-C.\textsuperscript{18} In the plasma, BHAC is converted into ara-C by $\omega$- and $\beta$-oxidation of the acyl moiety, and the resultant ara-C is transported into leukemic cells.\textsuperscript{11, 12, 18} In the cells, the subsequent ara-C is phosphorylated to ara-CTP thereafter. Again, ara-CTP is thought to be a key metabolite for the cytotoxic effect.\textsuperscript{18}

The importance of ara-CTP has been already shown clinically in high-dose ara-C therapies by Plunkett et al.\textsuperscript{19, 20} They demonstrated that ara-CTP was not predicted by the plasma ara-C pharmacokinetics, and that the therapeutic efficacy was closely correlated to the amount of ara-CTP. On the other hand, the significance of ara-CTP was seldom described in the conventional-dose ara-C or BHAC therapy because the previous detection methods for ara-CTP were less sensitive.\textsuperscript{21}

There are several reports on the pharmacokinetic study of BHAC, including ours.\textsuperscript{22-24} We have already reported the pharmacokinetics of the plasma BHAC and the plasma ara-C as a metabolite of BHAC, during a 90-min intravenous infusion of conventional-dose BHAC.\textsuperscript{24} In that study, BHAC was well maintained in the plasma and, at the same time, it was converted into ara-C slowly. Consequently, the plasma ara-C concentration was maintained continuously by BHAC administration. We proved that this deaminase-resistant prodrug worked as a long-acting ara-C.\textsuperscript{24}

If the intracellular ara-CTP is monitored simultaneously during BHAC therapy, the pharmacokinetic study may be more informative because the active metabolite of BHAC is ara-CTP. Furthermore, if the importance of ara-CTP is clinically demonstrated from
the viewpoint of the therapeutic efficacy of BHAC, the optimal BHAC therapy may be constructed based on the understanding of the ara-CTP pharmacokinetics.

Recently, we successfully monitored ara-CTP in leukemic cells of AML patients receiving low- or conventional-dose ara-C or BHAC by means of our new sensitive determination method.\(^{25, 26}\) In that preliminary report, we referred to the future direction that we would evaluate the relationship between the ara-CTP pharmacokinetics and the therapeutic outcome.\(^{26}\) Thus, in the present study, we integrated new patients and evaluated the ara-CTP pharmacokinetics viewing from the therapeutic response in AML patients receiving conventional-dose BHAC in the combination remission induction therapy.

MATERIALS AND METHODS

Chemicals and enzymes  ara-C, ara-CTP and bacterial alkaline phosphatase (EC 3.1.3.1) were purchased from Sigma Chemical Co. (St. Louis, MO, USA).  \(\text{Na}_2\text{HPO}_4\), acetonitrile, \(\text{NaCl}\), Tris, perchloric acid, KOH, and dextran were purchased from Nacalai Tesque. Inc. (Kyoto).  Tetrahydourididine was obtained from Calbiochem-Novabiochem Corp. (La Jolla, CA, USA).  Charcoal was purchased from J. T. Baker Chemical Co. (Phillipsburg, NJ, USA).  \([5-\text{H}]\)-ara-C (30 Ci/mmol) was purchased from Amersham International (Buckinghamshire, UK).  Anti-ara-C serum was kindly supplied by Asahi Chemical Industry Co., Ltd. (Tokyo).\(^{27}\)

Patients and treatments  Eleven patients eligible for the pharmacological studies were diagnosed as having AML (M1; 2 patients, M2; 7 patients, M4; 2 patients by
French-American-British classification) by the standard hematological and clinical criteria confirmed by the examination of bone marrow. They were 5 males and 6 females. Median age was 65 (range; 35-83). Informed consent for this investigation was obtained in advance. BHAC at 70 mg/m² was administered by intravenous infusion for 2 h twice daily in combination with 6-mercaptopurine (70 mg/m²), etoposide (70 mg/m²) and idarubicin (12 mg/m²) as remission induction therapy. Complete remission (CR) was considered established when blasts became less than 5% with normal levels of granuloid and erythroid series in bone marrow, and with normal levels of peripheral leukocytes and platelets.

**Sample collection** Blood samples were obtained before the therapy and after 0, 1, 2, 4, 6 and 10 h from the end of BHAC administration. The blood samples were then put into heparinized tubes containing tetrahydouridine, an inhibitor of cytidine deaminase, at a final concentration of 0.1 mM. The plasma and the mononuclear cells including leukemic blasts were fractionated by a Ficoll-Paque density centrifugation procedure. Both the plasma ara-C concentration and the ara-CTP concentration in leukemic cells were measured. In this study, we did not measure the plasma BHAC concentration because it was emphasized as a primary focus in our previous study.

**Determination of the plasma ara-C concentration** The plasma ara-C concentration was measured using the radioimmunoassay described by Shimada et al. with minor modifications. In brief, 50 µl of the plasma was mixed with 200 µl of 0.01 M phosphate buffer (containing 0.5% bovine serum albumin and 0.9% NaCl, pH 7.4), 50 µl of anti-ara-C serum, and 50 µl of [5-³H]-ara-C. The mixture was incubated for 16 h at 4 °C. Five hundred microliters of dextran-coated charcoal, which was composed of
100 mg of dextran and 1,000 mg of charcoal per 100 ml of the above phosphate buffer, was added to the mixture. The mixture was allowed to stand for 30 min at 4 °C, and centrifuged (1,000 x g, 15 min, 4 °C). The radioactivity of the supernatant was determined. The detection limit was 0.4 nM.

Determination of the intracellular ara-CTP concentration  The intracellular ara-CTP concentration was determined by the newly established method we previously reported.\textsuperscript{25)  }The nucleotide pool including ara-CTP was extracted from leukemic cells (2 x 10\textsuperscript{7} cells) using cold perchloric acid (final concentration 0.3 M), and then neutralized by KOH. ara-CTP was separated from the other nucleotides by high-performance liquid chromatography with an ion-exchange column, TSK gel DEAE-2 SW (250 x 4.6 mm inside diameter: particle size 5 µl: TOSOH Corp., Tokyo). The elution was performed with 0.05 M Na\textsubscript{2}HPO\textsubscript{4} (pH 6.9) - 20% acetonitrile at a constant flow rate of 0.7 ml/min at an ambient temperature. ara-CTP was monitored at 269 nm. The ara-CTP fraction was freeze-dried, dissolved again in 300 µl of 0.1 M Tris buffer (pH 10.1), and mixed with alkaline phosphatase (10 units). The mixture was incubated for 12 h at 55 °C, with the result that ara-CTP was dephosphorylated to ara-C. The ara-C derived from ara-CTP was measured using the radioimmunoassay described above. The obtained value of ara-CTP was divided by the packed cell volume occupied by the cell number (2 x 10\textsuperscript{7} cells) to determine the intracellular concentration. The detection limit was 20 nM.

Pharmacokinetic analysis  The area under the concentration-time curve from 0 to 24 h (AUC) and the pharmacokinetic parameters were obtained by moment analysis.\textsuperscript{30)
RESULTS

Our new sensitive method enabled the measurement of the low ara-CTP concentrations under 1 µM. The mean ± SD concentration-time curves of the plasma ara–C and the intracellular ara-CTP of all the patients are shown in Fig. 1. The pharmacokinetic parameters (mean ± SD values) are summarized in Table I.

Pharmacokinetics of the plasma ara-C and the intracellular ara-CTP  The plasma ara-C reached the maximal concentration ($C_{\text{max}}$) at the end of the infusion and decreased gradually thereafter. The intracellular ara-CTP reached the $C_{\text{max}}$ at 4 h from the end of the infusion and was eliminated gradually thereafter. The coefficient of variation of the $C_{\text{max}}$, the elimination half-life ($t_{1/2}$) and the AUC for ara-CTP were 74, 52, and 46%, respectively. Thus, the intracellular pharmacokinetics widely varied among patients. The $C_{\text{max}}$ and the AUC of the intracellular ara-CTP were not predicted from the respective parameters of the plasma ara-C (Fig. 2) ($p=0.79$ for the $C_{\text{max}}$, $p=0.66$ for the AUC, Spearman’s correlation test).

The comparison of the pharmacokinetics between CR and no response (NR) groups  Seven patients reached CR (CR group) while 4 did not respond to the treatment (NR group). The total dose of BHAC administered to each patient during the induction therapy was $1182 \pm 250 \text{ mg/m}^2$ (mean ± SD) in CR group, and $1026 \pm 80 \text{ mg/m}^2$ in NR group. Thus, there was no difference between the total doses in the two groups ($p=0.42$, Mann-Whitney test). The pharmacokinetic parameters were compared between them (Table I). The concentration-time curves of the plasma ara-C in the two groups appeared to be similar to each other (Fig. 3 A). The values for the
C_{\text{max}}, the AUC, and the t_{1/2} of the plasma ara-C were not different between these 2 groups. In contrast, the curve of the intracellular ara-CTP for CR group was drawn higher upon the curve for NR group (Fig. 3 B). The ara-CTP concentrations at all the time points including the C_{\text{max}} were higher in CR group than in NR group although the statistical difference was not found (p= 0.13 for the C_{\text{max}}, Mann-Whitney test). In addition, the ara-CTP was eliminated with the similar t_{1/2} values in the both groups. Consequently, the AUC of the intracellular ara-CTP was significantly greater in CR group than in NR group (p=0.02, Mann-Whitney test) (Fig. 4, Table I).

DISCUSSION

In the present study, we successfully monitored the intracellular ara-CTP concentrations during BHAC administration in the combination therapy. Moreover, we evaluated its pharmacokinetics from the viewpoint of the therapeutic efficacy. The ara-CTP pharmacokinetics widely varied among patients, and was not correlated to the plasma ara-C concentrations. The AUC of ara-CTP was significantly greater in CR group than in NR group, which was attributed to the higher ara-CTP concentrations achieved in patients with CR.

As shown in Fig. 1, BHAC maintained both the plasma ara-C and the intracellular ara-CTP for a long time. The t_{1/2} values of the plasma ara-C and the intracellular ara-CTP were longer, even compared with the historical values (2.8 h and 3.4 h, respectively) during a 2-h infusion of high-dose ara-C (3 g/m^{2}).^{31} BHAC prolonged the ara-C retention in the plasma because the drug is resistant to deamination and
converted into ara-C slowly.\textsuperscript{24)} Moreover, we demonstrated in our prior \textit{in vitro} study that the maintenance of ara-C in the medium was crucial to sustaining the intracellular ara-CTP in HL 60 leukemic cells.\textsuperscript{10)} As long as ara-C was present in the extracellular fluid, it was transported into the cells and phosphorylated to maintain ara-CTP, whereas the intracellular ara-CTP was rapidly eliminated if the extracellular ara-C was washed out.\textsuperscript{10)} Therefore, during BHAC therapy, the maintenance of ara-CTP in leukemic cells would be due to the prolonged retention of ara-C in the plasma. Thus, BHAC maintained both the plasma ara-C and the intracellular ara-CTP for a long time.

Yoshida et al. evaluated the ara-CTP pharmacokinetics during a 1-h infusion of high-dose BHAC (700 mg/m\textsuperscript{2}).\textsuperscript{32)} In their study, the C\textsubscript{max}, the t\textsubscript{1/2} and the AUC of ara-CTP were 0.081 µg/10\textsuperscript{7} cells (roughly equal to 20 µM), 13.6 h, and 1.224 µg \cdot h/10\textsuperscript{7} cells (roughly equal to 250 µM \cdot h), respectively. These values were compared with our pharmacokinetic results of 70 mg/m\textsuperscript{2} BHAC since in both studies BHAC was similarly administered as a short-hour infusion. To standardize the values, the C\textsubscript{max} and the AUC that were produced per 1 mg BHAC were calculated. The ratio values between the C\textsubscript{max} and the dose were 0.029 (calculated by the ratio of 20/700) for Yoshida et al. and 0.048 (3.42/70) for ours, which were close to each other. This ratio represents the relative height of the intracellular ara-CTP concentration achieved by 1 mg BHAC. The ratio values between the AUC and the dose were 0.36 (250/700) for Yoshida et al. and 0.43 (30.76/70) for ours, which were also very similar to each other. This ratio represents the amount of the intracellular ara-CTP produced by 1 mg BHAC, which is interpreted as the efficiency of the ara-CTP production. The t\textsubscript{1/2} values for both doses were also close to each other. Thus, these two doses produced ara-CTP with the
same efficiency despite the 10-fold difference. This suggests that ara-CTP would be generated in a dose-dependent manner and this ara-CTP production would not be saturated by the doses at least up to 700 mg/m$^2$.

Conventional-dose BHAC is usually used at the doses from 150 to 200 mg/m$^2$. In our protocol, 140 mg/m$^2$ BHAC was used per day. This dose was divided into halves and the half dose (70 mg/m$^2$) was infused twice daily. Thus, the daily dosage (140 mg/m$^2$/day) is regarded to be conventional. Strictly speaking, we analyzed the pharmacokinetics of BHAC at 70 mg/m$^2$, substantially half the conventional dose. However, the pharmacokinetic data described in our study would be applicable to the conventional dose because the same efficiency of the ara-CTP production was suggested at the doses between 70 mg/m$^2$ and 700 mg/m$^2$.

ara-CTP has been already reported as a crucial determinant during high-dose ara-C therapies (3 g/m$^2$). Plunkett et al. demonstrated that the greater AUC of ara-CTP was closely correlated to the successful therapeutic outcome during a 2-h infusion of 3 g/m$^2$ ara-C. They showed that the t$_{1/2}$ of ara-CTP was significantly longer in patients with CR whereas no difference was found in the C$_{max}$ between CR and NR groups. This suggested that the greater AUC of ara-CTP in CR group was mainly attributed to the longer ara-CTP retention in leukemic cells. On the contrary, in our present BHAC study, the AUC of the intracellular ara-CTP was significantly greater in CR group, but the t$_{1/2}$ values were not different between the two groups. The greater AUC of ara-CTP during BHAC therapy was mainly due to the higher ara-CTP concentrations achieved in leukemic cells. It would be difficult to compare directly between these two therapies because the drugs, the doses, and the backgrounds of the patients were different from
each other. However, as the intracellular metabolism of ara-C, deoxycytidine kinase is thought to be a key enzyme for the production of ara-CTP, while cytidine deaminase is regarded to be responsible for the degradation.\textsuperscript{7, 9, 34} If so, the mechanism of the drug resistance may be different between the 2-h infusions of BHAC and ara-C.

In contrast to the intracellular behavior of ara-CTP, no difference was found in the plasma ara-C pharmacokinetics between CR and NR groups. In addition, the total doses of BHAC administered through this combination induction therapy were not different between the two groups. In other words, leukemic cells in both groups were equally loaded with the same quantity of the AUC of the plasma ara-C in the same manner. Thus, it is suggested that the difference of the ara-CTP production would be mainly up to the nature of leukemic cells.

The Japan Adult Leukemia Study Group (JALSG) compared the therapeutic effect between BHAC and ara-C in the combination induction therapy for AML patients in a large cohort study.\textsuperscript{35} In that study, conventional-dose ara-C (80 mg/m\textsuperscript{2}) was given as a continuous intravenous infusion while 200 mg/m\textsuperscript{2} BHAC, the equivalent dose of 80 mg/m\textsuperscript{2} ara-C, was used as a 3-h intravenous infusion once daily. The study concluded that BHAC resulted in poorer CR and lower event-free survival rates than ara-C. Regarding ara-C, however, many pharmacokinetic studies had been previously conducted, which revealed that the continuous ara-C infusion produced ara-CTP most effectively, and therefore it was the best administration schedule for ara-C.\textsuperscript{19, 20} Conversely, BHAC has been used empirically as a 3-h infusion once daily, only because its cytotoxic effect was reported to be independent of the treatment schedule in animal tumor models.\textsuperscript{11, 12, 15-17} The retrospective analysis of this comparative study
also suggested that BHAC was not equivalent to ara-C in terms of the cytotoxic intensity despite the premise that the doses of both agents were adjusted to be equivalent by their respective molecular weights.\textsuperscript{36} At least, our present findings suggest that BHAC should be given twice daily because the t\textsubscript{1/2} of ara-CTP is almost half a day. Thus, if the better schedule for BHAC is found based on the clinical pharmacokinetics of ara-CTP, it may provide a different result for the comparison between BHAC and ara-C.

ara-CTP has been reported to be a crucial parameter for the prediction of the therapeutic efficacy of high-dose ara-C therapy.\textsuperscript{19, 20} On the other hand, the importance of ara-CTP has not been clinically confirmed yet with regard to BHAC therapy. This is the first report to relate the clinical pharmacology of ara-CTP to the therapeutic response during BHAC treatment. It would be more accurate to evaluate the clinical response of the single therapy of BHAC alone. But it is difficult because BHAC is usually combined with other antileukemic agents in the treatment of AML. Nevertheless, the present pharmacokinetic results strongly suggest that intracellular ara-CTP concentration can be a predictor for the response to the BHAC–based combination therapy. ara-C is thought to inhibit DNA synthesis partly through the inhibition of DNA polymerases by ara-CTP and partly through the incorporation of the drug into DNA strands. Even for the latter, the formation of ara-CTP is essential. ara-CTP inhibits DNA polymerases dose-dependently competing with deoxycytidine 5’-triphosphate.\textsuperscript{6} It would be possible to predict the degree of inhibition of DNA polymerases by a given ara-CTP concentration from a knowledge of the kinetic parameters of DNA polymerases including Michaelis constant and the inhibition constant and the intracellular ara-CTP and deoxycytidine triphosphate concentrations.\textsuperscript{6}
The inhibition constant values for polymerases $\alpha$ and $\beta$ for ara-CTP are reported to be 1.5 µM and 8 µM, respectively in primary AML cells.\(^{38}\) These in vitro values cannot be directly translated in the clinical situation.\(^6\) However, it is suggested that individual leukemic cells might have a target ara-CTP concentration for the maximal inhibition of DNA synthesis. Thus, for the maximal therapeutic effects, the optimal administration schedule for BHAC may be directed by the intracellular ara-CTP pharmacokinetics in each patient.

**ACKNOWLEDGMENTS**

This work was supported in part by a Grant-in-Aid from the Ministry of Health and Welfare, Japan. We thank Ms. Shinobu Niwa for her technical assistance.
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21)


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LEGENDS

Fig. 1. Mean ± SD concentration-time curves of the plasma ara-C (A) and the intracellular ara-CTP (B) in 11 acute myelogenous leukemia patients who received the 2-h intravenous infusion of 70 mg/m^2 BHAC.

Fig. 2. Relationship of the C_{max} (A) or the AUC (B) between the plasma ara-C and the intracellular ara-CTP.

Fig. 3. Mean concentration-time curves of the plasma ara-C (A) and the intracellular ara-CTP (B) in CR group (7 patients) and NR group (4 patients) receiving the 2-h intravenous infusion of 70 mg/m^2 BHAC. Closed circles: CR group; open circles: NR group;

Fig. 4. Comparison of the AUC of the plasma ara-C (A) or the intracellular ara-CTP (B) between CR group (7 patients) and NR group (4 patients).
A

B

ara-C (µM) vs Hours

ara-CTP (µM) vs Hours
A

ara-C AUC (µM•h)

B

ara-CTP AUC (µM•h)
### Table I. Mean ± SD Values of Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th></th>
<th>ara-C</th>
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<tr>
<td></td>
<td>$C_{\text{max}}$</td>
<td>AUC (µM)</td>
<td>$t_{1/2}$ (h)</td>
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<td>Mean</td>
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<td>0.84</td>
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<td></td>
<td>SD</td>
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<td>NR group</td>
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<td></td>
<td>SD</td>
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Abbreviation: ara-C: 1-β-D-arabinofuranosylcytosine; ara-CTP: 1-β-D-arabinofuranosylcytosine 5'-triphosphate; $C_{\text{max}}$: maximal concentration; AUC: area under the concentration-time curve; $t_{1/2}$: elimination half-life; CR: complete response; NR: no response.