Suitable Effective Mode of Administration of Intravenous Ara-C in Acute Leukaemias

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Introduction

Ara-C (the shortest form of ARabinofuranosyl Cytidine, also known as cytosine arabinoside, arabinocytosar, arabinosyl cytarabine or, simply, cytarabine) is a common chemotherapeutic agent used in haematological malignancies.

Ara-C is a commonly used drug in acute leukaemias. In different stages of treatment dose and mode of administration of this drug is variable. It is usually considered as a cell cycle specific drug, but except in ‘standard’ induction of remission therapy for acute myelogenous leukaemia it is not usually given by continuous infusion in other conditions. This article discusses about the different intravenous modes of administration of Ara-C in AML induction chemotherapy, their outcomes, and urges for trials to find out a suitable mode of administration of this common drug.

Keywords: cytosine arabinoside, arabinocytosar, arabinosyl cytarabine, Ara-C, cytarabine

ABSTRACT

Ara-C is a commonly used drug in acute leukaemias. In different stages of treatment dose and mode of administration of this drug is variable. It is usually considered as a cell cycle specific drug, but except in ‘standard’ induction of remission therapy for acute myelogenous leukaemia it is not usually given by continuous infusion in other conditions. This article discusses about the different intravenous modes of administration of Ara-C in AML induction chemotherapy, their outcomes, and urges for trials to find out a suitable mode of administration of this common drug.

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Figure 1 Cell cycle. G1 and G2 (gaps) are times between completion of M-phase and start of S-phase and between completion of S-phase and start of M-phase, respectively.¹ Ara-C acts at S phase.

Ara-C is considered a cell-cycle specific drug acting in synthetic (S) phase (Figure – I) of cell division only.² That is why it is being used by continuous infusion over 7 days in the ‘standard’ induction of remission chemotherapy for acute myeloid leukaemia (AML).³⁻⁷ In many centres in Bangladesh the continuous 168 hours of infusion is difficult to maintain, and, for practical purpose, the mode of administration is usually cut short somewhere between 12-24 hours daily.⁸⁻¹⁰

On the other hand, in the United Kingdom Medical Research Council Acute Myeloid Leukaemia (UK MRC AML) trials the mode of administration is...
intravenous push of standard dose Ara-C (100 mg/m2 body surface area per day), twice daily for 10 days (i.e. intravenous push instead of infusion and 20 standard doses of ara-c).¹¹⁻¹⁴ UK MRC AML Trials are the largest trials in the world for treating AML patients, recruiting and following up thousands of subjects for several years in several countries. Moreover, high dose Ara-C (HiDAC), in the consolidation phase of treatment for AML patients or in the treatment of non-Hodgkin lymphoma (NHL) (especially with central nervous system involvement), or intermediate dose Ara-C (IDAC) are administered over 1-3 hours infusion only.⁵⁻¹⁵ Conventional dose Ara-C used in chemotherapy schedule for ALL (e.g. in BFM-95 trial, UKALLXI), is also given over 1 hour to a few hours only.²¹⁻²³

To clarify these discrepancies in the mode of administration of intravenous Ara-C texts and articles were searched for.

**Pharmacology of Ara-C:**

Ara-C is a pyrimidine analogue with terminal elimination half-life is 2–6 hours.² Pyrimidine is a nucleotide; and nucleotide analogues are antimetabolites that share the common mechanism of action, i.e., binding to DNA and its synthetic enzymes & inhibiting normal process of synthesis of DNA. Inhibiting synthesis of DNA hampers division and proliferation of malignant cells. Pharmacologically Ara-C is a prodrug, it needs to be converted to the active form Ara-CTP (Ara-C triphosphate) before binding to DNA. This active form is also continuously being broken down within cells. That is why, the ultimate effect of ara-c depends on persisting level of Ara-CTP, not Ara-C, within the cell.²⁴ Laboratory experiments by Silagi in 1965 revealed irreversible inhibition of mitosis and DNA synthesis after treatment with Ara-C for as little as 2 hours at 10 μg/ml dose in mouse fibroblasts in culture media.²⁵ It means, though Ara-C shows its anti-cancer effects during synthetic phase of cell cycle, exposure of cells for merely 2 hours is enough, because it is taken up by the cells and converted to its active form which persists for few hours within the cell.

For high dose Ara-C, there are some additional mechanisms of action as revealed by intracellular
biochemical analysis. Investigators found modification in metabolic pathways and change in metabolic biomarkers.

**Other cell cycle specific drugs:**

Interestingly, there are many other common anti-cancer drugs used in acute leukaemias which are cell cycle specific but are not given by continuous drip. For example, 5-Fluorouracil is a fluoropyrimidine analogue (terminal elimination half-life 10-20 minutes), cell cycle–specific with activity in the S-phase; but it is given as intravenous bolus injection. Clofarabine (terminal elimination half-life 5 hours) is also active in S phase and given IV over 2 hours daily for 5 days. Etoposide (elimination half-life 3-10 hours) is also a cell cycle specific drug active at late S- and G2-phases, but is given over 1-hour infusion. Vinca alkaloids (vincristine, vinblastine, and vinorelbine; plasma terminal half-lives are about 85 hours, 25 hours and 27-43 hours, respectively) act only in metaphase, which is of course the shortest period of cell cycle. They are given as rapid push over 1 minute in a side port of a free-flowing IV line. Decitabine, a cell cycle specific purine analogue, is given 20 mg/m2 intravenously over 1 hour. Many anti-cancer drugs used in solid cancers are also cell cycle specific. For example, gemcitabine, is a pyrimidine analogue like Ara-C (half-life 4-10 hours) but is given over 30 minutes. Docetaxel (terminal half-life 11 hours), active only in mitotic (M) phase, is given over 1 hour. So, the traditional idea that Ara-C is to be given by continuous infusion in the induction of remission phase of acute myeloid leukaemia might not be a hard and fast rule.

**Continuous infusion versus intravenous push in AML in clinical practice:**

The continuous infusion of Ara-C in AML induction was established by a series of Cancer And Leukemia Group B (CALGB) trials in USA in 1980s and there are other studies that showed continuous infusion is superior to intravenous push injection. Despite these evidences UK MRC AML trials continue to practise intravenous push of Ara-C. Intravenous push Ara-C is not practised in induction chemotherapy for AML in this country, but a small study based on UK MRC AML trials was conducted in Bangabandhu Sheikh Mujib Medical University (BSMMU). The study tested intravenous push Ara-C 100 mg/m²/12 hour for 10 days (20 doses) along with etoposide (75 mg/m²/d, maximum 100 mg) for 5 days and daunorubicin (45 mg/m²/d), for 3 days. Initially there was suspicion whether standard dose intravenous push Ara-C would induce adequate cytoreductive effect or not, but the investigators found prolonged grade 4 neutropenia (ANC 0/mm³ for as long as 4 days), and complete remission in all alive patients, though death rate was 33%. Table 1, 2 and 3 summarize the outcome of some studies using intravenous infusion and intravenous push of standard dose Ara-C in AML patients.

**Table 1. Summary of outcome of studies using Ara-C infusion in induction therapy for AML patients (all consisted daunorubicin also)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Complete remission (%)</th>
<th>Partial remission (%)</th>
<th>Not in Remission (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Islam 2012</td>
<td>40</td>
<td>24</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Yates, et al. 1982</td>
<td>72</td>
<td>2</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Dillman et al. 1991</td>
<td>64</td>
<td>7</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Pagnano et al., 2006</td>
<td>63.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bishop 1999</td>
<td>56.74</td>
<td>—</td>
<td>—</td>
<td>10.15</td>
</tr>
<tr>
<td>Ashrafi et al., 2013</td>
<td>58.9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tsunumi et al., 2007 (elderly)</td>
<td>73</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Irshadullah 2016</td>
<td>33</td>
<td>27</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>Robak and Wierzbowska 2009 (elderly)</td>
<td>—</td>
<td>20-40</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Bairón-Santiago, et al., 2010</td>
<td>62.7</td>
<td>23.2</td>
<td>—</td>
<td>13.9</td>
</tr>
</tbody>
</table>

DOI: https://doi.org/10.37545/haematoljbd202286
Table 2. Summary of outcome of studies using Ara-C infusion in induction therapy for AML patients (all consisted an anthracycline and etoposide)

<table>
<thead>
<tr>
<th>Study</th>
<th>Complete remission (%)</th>
<th>Partial remission (%)</th>
<th>Not in Remission (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sackmann-Muriel et al., 1996</td>
<td>80.9</td>
<td>4.4</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>Lowenthal et al., 1999</td>
<td>80</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Pierri et al., 1999</td>
<td>57</td>
<td>29</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Archimbaud et al., 1999</td>
<td>59</td>
<td>32</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Summary of outcome of studies using Ara-C as intravenous push in induction therapy for AML patients (etoposide for 5 days and daunorubicin for 3 days added in all the studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Complete remission (%)</th>
<th>Partial remission (%)</th>
<th>Not in Remission (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irsahadullah 2016</td>
<td>67</td>
<td>—</td>
<td>—</td>
<td>33</td>
</tr>
<tr>
<td>UK MRC AML 10</td>
<td>74</td>
<td>—</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>UK MRC AML 12</td>
<td>78</td>
<td>8</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>UK MRC AML 15</td>
<td>83</td>
<td>4</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

These studies show that the complete remission after using intravenous push Ara-C is comparable to that of continuous Ara-C infusion; especially in Table 2 and 3, where 3 drugs were used. These results negate the suspicion that being a cell cycle specific drug, Ara-C in intravenous bolus dose should not be effective and must be given as continuous infusion.

Intermediate dose Ara-C (500 mg·1 g/m²) IV bolus 12 hourly was used as post-remission salvage therapy in elderly patients without any apparent benefit.41

**Conclusion:**

Developed countries concentrate on discovery of new drugs for better response in patients with cancer. These drugs are very costly and, to a large extent, not available beyond clinical trials. Patients of developing countries are far away from getting benefit from these trials. Developing countries like ours should design their own trials comparing various doses and modes of administration of established, cheaper and easily available drugs in various combinations to reveal suitable mode of administration of drugs. For example, if intravenous push of Ara-C is found to be of comparable efficacy to continuous infusion for 168 hours in AML induction therapy in large studies, there is no need to pursue for the latter in resource poor facilities with undocumented deviations from written ‘standard’ protocols. This will also give some comfort to the patient’s hospital stay. Intravenous push can also be planned for rare stable patients with acute leukaemias as day care basis till cytopenia ensues, then the patient can be admitted to the hospital, reducing total hospital stay period. Trials with higher dose intravenous push may also be planned in resistant cases and in patients with acute leukaemias with adverse cytogenetics, with other established drugs in practice, instead of costly newer or investigational drugs. We should sincerely consider planning this sort of trials in our country.

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Haematol J Bangladesh 2022;6(1):30-37


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system involvement), or intermediate dose Ara-C 12-24 hours daily.8-10

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aml/17/web/files/new5/AML%2017%20Protoc

Acute Myeloid Leukaemia Or High Risk


DOI:


