The Pharmacologic Basis for the Efficacy of High-Dose Ara-C and Sequential Asparaginase in Adult Acute Myelogenous Leukemia

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Dose-related effects of ara-C include overcoming a relative transport impediment in human leukemia cells. This result then allows intracellular metabolism and incorporation into DNA to proceed to the maximum extent possible. In addition, the increased synthesis of ara-CDP-choline associated with these high doses may serve as an alternate substrate for phosphatidyl choline synthesis, which may contribute to membrane fragility and cell lysis.

HiDAC also serves as a "prodrug" for high concentrations of ara-U, which in turn diminishes ara-C catabolism with a prolonged γ phase of systemic clearance and also causes cytostasis in S-phase with enhanced anabolism and cytotoxicity of subsequent doses of ara-C. This metabolite/drug interaction could be termed "self-potentiation," a feature which contributes to the overall activity of HiDAC. Asparaginase enhances these effects in a schedule-dependent fashion by lowering the cellular pool size of dCTP and consequent enhanced metabolism of ara-C. The therapeutic benefit of these pharmacologic manipulations has been verified in a randomized clinical trial in patients with acute myelogenous leukemia.

The evolution of therapeutic practice in clinical oncology has been largely based on empirical trial and error, especially with respect to selection of a drug, its dose, schedule, and use in combination chemotherapy. One of the hallmarks of Dr. Bertino's career has been the utilization of laboratory observations regarding our understanding of cellular biochemistry, mechanisms of drug action, drug resistance, and drug-drug interactions in the rational design of therapeutic regimens. This integration of the laboratory with clinical trials has obviously influenced many of us who trained with Joe, as is evident in the presentations today. In this regard, I'd like to describe some of our recent laboratory and clinical investigations with ara-C and asparaginase in acute leukemia.

The department of pharmacology at Yale contributed a lot to the early development of cytosine arabinoside (ara-C). Glenn Fischer, Ming Chu, Dick Momparler, Arnold Welch, Bill Creasy, Rose Papac, and Paul Calabresi, among others, were involved in studies of the pre-clinical and clinical pharmacology of ara-C as well as in clinical trials.

Abbreviations: AML: acute myelogenous leukemia Ara-C: cytosine arabinoside, 1-β-D-arabinosyl cytosine, Cytarabine, Cytosar-U® Ara-CDP-Choline: arabinosyl cytosine diphosphocholine Ara-CMP: monophosphate of arabinosyl cytosine Ara-CTP: triphosphate of arabinosyl cytosine Ara-U: uracil arabinoside, 1-β-D-arabinosyl uridine ASNase: asparaginase CALGB: Cancer and Leukemia Group B CTP: cytidine triphosphate dCTP: deoxyctydine triphosphate dCyd: deoxyctydine HiDAC: high-dose ara-C NBMPR: nitrobenzyl mercaptapurine riboside SDAC: standard dose ara-C

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Figure 1 details the cellular pharmacology of ara-C. Chu and Fischer had shown that in order to exert its effect, ara-C had to be metabolized to the nucleoside triphosphate of arabinosyl cytosine (ara-CTP) [1]. Others then showed that cytotoxicity from ara-C was linked to its incorporation into DNA [2,3]. Subsequently, various resistance mechanisms in experimental cell lines were delineated, including diminished anabolism to ara-CMP mediated by deoxycytidine kinase [4], expanded deoxycytidine triphosphate (dCTP) pools [5], and short intracellular half-life of ara-CTP [6]. In these same experimental cell lines, the process of membrane translocation or transport was found to be extremely rapid and, therefore, considered not to be an important parameter in the cellular pharmacology of ara-C.

Ara-C enters the cell by a carrier-mediated facilitated diffusion mechanism common to nucleosides [7]. A clear distinction must be made between the physiological processes termed transport and uptake. For the present discussion, transport will refer to the carrier-mediated membrane translocation of the drug. While “uptake” also invokes “transport,” the usual measurements which describe this process primarily speak to cellular accumulation. Thus, in the present discussion, the term “accumulation” will refer to the intracellular metabolism and retention of ara-C and its metabolites. While membrane transport of ara-C in experimental tumor models has been shown to be rapid and not a limiting factor in ara-C metabolism by these cells [8], it has recently been demonstrated that human leukemia cells taken directly from patients have, in comparison, very low nucleoside transport activity [9,10].

Over the past several years, as part of a global program of studies of the pharmacology of ara-C in human leukemia cells, we have been conducting a prospective study of ara-C transport and metabolism in patients with acute leukemia at diagnosis and relapse. These studies intend to relate these pharmacological parameters to drug response and resistance and, in turn, could be useful for subsequent clinical trial design.

The number of nucleoside carrier molecules per cell may be directly quantitated by measuring the binding capacity for the high-affinity inhibitor, nitrobenzyl-mercaptopurine riboside (NBMPR) [11]. NBMPR is a purine nucleoside analog which binds...
Thus, approaches everyday achievable plasma concentrations strikingly experimental molecules (NBMPR, CEM) and alternative indicated molecules in human leukemic blasts insensitively nucleoside by [13].

Transport To essence, this transport human and is the sole determinant of ara-C [11]. Because some experimental cell lines may have significant NBMPR-insensitive nucleoside transport capacity, NBMPR is also a useful tool for elucidating alternative transport routes [12].

Transport rates and the number of NBMPR sites, that is, nucleoside carrier molecules in human leukemic blasts from patients, are contrasted with several murine and human experimental cell lines in Table 1. Consistent with previous studies, which indicated that transport was not rate-limiting in ara-C pharmacology, the number of NBMPR sites and ara-C transport rates are high in both murine and human leukemia experimental cell lines, including myeloid (HL-60, ML-1) and lymphoblastic (CCRF-CEM) leukemias. In contrast, the number of NBMPR binding sites (that is, transport molecules) and ara-C transport rates in leukemic blasts taken directly from patients is strikingly lower [13].

To assess the practical relevance of lower transport activity in human leukemia cells, the transport "control strength" was determined (Fig. 2). Transport control strength, in essence, is an expression of the role of transport as a determinant of the rate of net intracellular accumulation of ara-C metabolites. When transport is in great excess and not a factor of consequence, the control strength is zero. When the rate of transport is slow and is the sole determinant of the rate of net accumulation, control strength is one [13].

Transport control strength is dependent on the extracellular concentration of ara-C. The Km for ara-C transport is 400 μM, a value that is quite high compared to clinically achievable plasma drug concentrations (see below). Thus, for practical purposes in everyday therapeutics, the transport rate will be approximately proportional to the plasma concentration. In contrast, the rate of ara-C phosphorylation intracellularly approaches a maximal velocity at relatively lower drug levels in the range of 2–5 μM. Thus, at concentrations below 1 μM, transport may be rate-limiting, but as the concentration is increased and phosphorylation approaches a maximum, the ratio of

| Table 1: Ara-C Transport Rate and Nucleoside Carrier Sites |
|-------------------------------------------------------------|
| 1. Patients | Rate* | NBMPR Sites |
| Acute leukemia | 14 ± 15 | 4,223 ± 4,334 |
| n = 45 | n = 61 |
| 2. Human leukemia in cell culture | | |
| ML-1 | 805 | 139,000 |
| HL-60 | 49 | 59,000 |
| CCRF-CEM | n.d. | 183,000 |
| 3. Mouse ascites tumors | | |
| Ehrlich | 272 | 94,000 |
| L5178Y | 105 | 74,000 |
| P388 | n.d. | 137,000 |

*pmol/min/10^6 cells at 50 μM [3H] ara-C ± SD
Maximal specific [3H]NBMPR binding sites per cell ± SD
n.d. = not determined
Reproduced from [13]
transport capacity to phosphorylation capacity increases. At high extracellular concentrations, ara-C transport is in excess. This relationship is illustrated by several examples depicted in Fig. 2. The solid line is based on transport and accumulation data for 45 patients. This line shows that, for the majority of patients, membrane transport is the rate-limiting process at ara-C concentrations typical of those achieved during continuous infusion of standard dose ara-C (SDAC), that is, <1.0 μM. As the extracellular concentration of ara-C is increased to the 10–20 μM range, however, transport is less important as a determinant of the accumulation rate. As noted below, the extracellular (plasma) concentrations achieved during short-term infusions of high-dose ara-C are in considerable excess of these levels. The dashed and dotted curves illustrate the extremes of this process. Transport is the major rate-determining process for the patient’s cells represented by the dashed line up to 8 μM ara-C. For the patient’s cells represented by the dotted line, transport control strength is always less than 0.5, indicating that transport only partially determines the rate of uptake for this patient even at low ara-C concentrations [13].

The practical message from these studies is that for most patients membrane transport is the rate-limiting step in the cellular accumulation of ara-C at plasma concentrations of drug typical of that achieved with standard doses and that this impediment may be obviated by a suitable increase in dose, which will provide plasma concentrations above 10 μM. At these concentrations, the capacity of the cell to phosphorylate ara-C and the extent of its incorporation into DNA will be the determinant features of ara-C cytotoxicity. Thus, any means for enhancing these latter processes such as the lowering of the competing dCTP pools by biochemical modula-
tion [14,15] or the accumulation of cells in S-phase by the use of cytostatic agents [16] may enhance the effects of ara-C. To some extent, these latter mechanisms may be invoked by uracil arabinoside (ara-U)/ara-C [17,18] and asparaginase (ASNase)/ara-C interactions [19], as noted below.

For a moment, let us turn to the clinical use of ara-C. The sole clinical indication for ara-C is in the treatment of acute leukemia. In this regard, it is commonly administered as a continuous infusion or twice daily injection for seven days, at a daily dosage of 100 to 200 mg/m², so-called standard dose ara-C (SDAC). Used as a single agent, this dose and schedule will result in complete remission in 25 percent of previously untreated patients [20]. Thus, aside from the 20 percent of patients who die during induction, most of the patients at presentation may be said to have natural drug resistance to these doses. Most of the patients who enter remission will eventually relapse; since response rates are lower in this group of patients, they may be said to have developed acquired drug resistance.

The introduction of high-dose ara-C (HiDAC) in the treatment of acute leukemia [21] was based on theoretical assumptions derived from available data on ara-C pharmacology [22]. These observations questioned whether the plasma concentrations of ara-C following the administration of standard doses were sufficient to achieve maximum therapeutic benefit from the drug [22]. The subsequent clinical testing of these concepts was first conducted here at Yale. This simple study showed that a 15–30-fold dose escalation could elicit a renewed therapeutic response in patients who were clearly refractory not only to SDAC but also to other antileukemic drugs [21]. This observation lent currency to theory [22]. The utility of this therapeutic maneuver has subsequently been validated by others [23–25]. Given this efficacy of HiDAC when SDAC has failed raises the question as to what the “optimal or standard dose” of ara-C should be for routine practice.

The cellular pharmacokinetics of ara-C described above (transport and accumulation) are influenced by systemic pharmacokinetics. Plasma drug levels achievable during bolus and continuous infusion of various doses of ara-C are shown in Table 2. Bolus injection of 100 mg/m² results in peak plasma levels of approximately 20 μM [26]. Because of rapid clearance of the drug from plasma, however, this level drops to 1 percent within two hours [26]. Thus, the duration of exposure of the leukemic cells to extracellular concentrations of ara-C capable of overcoming transport deficits (Fig. 2) would be relatively brief. Continuous infusion of 100 and 200 mg/m² (SDAC) results in average plasma steady-state concentrations of 0.4 and 0.8 μM, respectively [26,27].

Again in consideration of the data relating the effect of transport on cellular metabolism at various drug concentrations, the plasma steady-state values achieved

| TABLE 2 |
| Plasma Levels of Ara-C |
| --- |
| µM | Reference |
| 100 mg/m² |
| Bolus | 20.0 | [26] |
| Continuous infusion | 0.4 | [26] |
| 200 mg/m² |
| Continuous infusion | 0.8 | [27] |
| 3,000 mg/m² | 100.0 | [28] |
with SDAC would benefit fewer patients, perhaps explaining the observed 25 percent complete remission frequency associated with the use of SDAC [20]. In contrast, plasma steady-state levels achieved during infusion of 3 g/m² ara-C administered every 12 hours for four doses. Points represent the mean ± SD of 20 studies in four patients (▲—▲ — ara-C) and (●—● — ara-U) (reproduced from [28]).

At the conclusion of administration of ara-C, either bolus dose or infusion, the initial plasma clearance rates (α and β half-lives) are fairly comparable at each dose level. The plasma clearance of SDAC has been described as a bi-exponential process [29]. With infusions of high-dose ara-C at 3 g/m², however, most patients display a tri-exponential process with an additional γ half-life of six hours (Fig. 3) [28]. Shortly after the start of infusion, ara-C is rapidly deaminated to ara-U, which is relatively nontoxic. During HiDAC infusion, the plasma concentration of ara-U is two to three times higher than ara-C, ranges between 200 and 300 μM, and displays a mono-exponential half-life of 3.75 hours (Fig. 3) [28]. Clinical and laboratory observations suggest that the extent of this deamination process is dose-dependent. Ho and Frei measured the ara-U/ara-C ratio in plasma following various doses of ara-C. At doses ranging from 47 to 200 mg/m², the ara-U/ara-C ratio at five minutes after drug administration was 2.6 to 1.4, respectively [30]. In contrast, this ratio dropped to 0.3 following 1,500–3,000 mg/m² [30]. Following up this lead, we studied the effect of high concentrations of exogenous ara-U on ara-C catabolism in vitro and in vivo. A Lineweaver-Burk plot (Fig. 4) illustrates this interaction in vitro. The addition of increasing concentrations of ara-U retarded the activity of cytidine deaminase on ara-C. The enzyme was derived from human leukemia cells [28]. With continuous infusion in mice, ara-U is concentrated in the liver and kidneys; assay of CR deaminase

![Plasma ara-C and ara-U concentrations during and after a three-hour infusion of 3 g/m² ara-C administered every 12 hours for four doses. Points represent the mean ± SD of 20 studies in four patients (▲—▲ — ara-C) and (●—● — ara-U) (reproduced from [28]).](image-url)
SUBSTRATE CONCENTRATION VERSUS REACTION VELOCITY

FIG. 4. Lineweaver-Burk plot indicating the inhibitory effect of ara-U on purified cytidine deaminase derived from human AML cells. The enzyme assays were performed as described in materials and methods, using 0.7 unit of purified Cyd deaminase and the indicated concentrations of ara-U. The insert (B) shows a replot of the slope of the lines obtained from the double reciprocal plot (A) versus ara-U concentration (reproduced from [28]).

activity in these organs shows decreased activity following ara-U infusion [18]. The plasma clearance of ara-C administered after infusion of ara-U for 48 hours is retarded relative to saline-infused mice [18]. We conjecture that a similar occurrence in man contributes to the observed \( \gamma \) phase.

The most successful clinical reports of the use of high-dose ara-C utilize 6–12 consecutive doses [31]. Given the relatively long plasma half-life for ara-U [28], the repetitive doses of HiDAC at 12-hour intervals, in essence, mimic a continuous infusion of large doses of ara-U. We thus decided to explore the direct effects of ara-U on murine leukemia cells. When exposed to high concentrations of ara-U, that is, \( 10^{-5} \)–\( 10^{-3} \) M, the growth of L5178Y cells was delayed. DNA histogram analysis of these growth-inhibited cells revealed accumulation in the S-phase of the cell cycle (Fig. 5). Studies with these cell populations showed an overall increase in the specific activity of the S-phase enzyme deoxycytidine (dCyd) kinase and, consequently, exposure of the cells to ara-C after ara-U pretreatment for 24–48 hours was associated with increased ara-CTP and ara-C DNA formation, with a consequent increase in ara-C cytotoxicity [17]. Similar effects have been noted in vivo with the continuous infusion of large doses of ara-U, followed by ara-C treatment [18].
One of the most striking features associated with the clinical use of high-dose ara-C is the rapid lysis of leukemia cells. Within 72–96 hours of having started HiDAC therapy, the peripheral blood count has commonly been reduced to 1 percent of its original number. This clinical observation raised a question regarding the mechanism(s) of ara-C cytotoxicity. If ara-C destroys cells only subsequent to its incorporation into DNA, 99 percent of the cells will not have all traversed S-phase during this time [32]. Review of the metabolism of ara-C suggests the possible implication of a heretofore trivial metabolite of ara-C, arabinosyl cytosine diphosphocholine (ara-CDP choline) [33,34] in this cell lysis mechanism. Ara-CTP can serve as a substrate in the synthesis of ara-CDP-choline. The subsequent utilization of ara-CDP-choline as a substrate for, or as an analog inhibitor in, the synthesis of phosphatidyl choline may cause sufficient imbalance in phospholipids in the cell membrane to result in membrane fragility. We are pursuing this hypothesis with current laboratory studies [35].

Well, what does all of this have to do with current therapeutics? As mentioned earlier, the prime clinical indication for ara-C is in the treatment of acute leukemia. In this regard, new drugs enter clinical trials by first being tested in a phase II fashion in
patients with relapsed and refractory acute myelogenous leukemia (AML). Review of response rates of some newly introduced drugs reveals overall response rates in the 15–20 percent range [36]. In this setting, review of high-dose ara-C efficacy in patients who were either refractory or who had relapsed from SDAC therapy revealed response rates in the 25 percent range following the use of HiDAC; that is, response rates equal to those of newly introduced drugs (Table 3) [31]. This renewed response from HiDAC

CALGB 8121

FIG. 6. CALGB protocol 8121 using sequential high-dose ara-C (HiDAC) and asparaginase (ASNase) or HiDAC alone: 3 g/m² of ara-C was added to 500 cc of preservative-free saline and infused intravenously over three hours. The dose was repeated every 12 hours for four doses. Three hours after the completion of the fourth dose, a single intramuscular injection of 6,000 IU/m² ASNase was administered. The same treatment was repeated on days 8 and 9. By random allocation, an equivalent group received the same dose and schedule of HiDAC without the ASNase (reproduced from [38]).
in patients who had already failed therapy with lower doses of ara-C may invoke
dose-response relationships such as membrane transport, altered pharmacokinetics,
ara-U/ara-C interactions, and possibly alternate mechanisms of action such as
interference with cell membrane integrity.

Our prior laboratory data indicate that high-dose ara-C is potentiated by the protein
synthesis inhibitor asparaginase in a schedule-dependent fashion [37]. Since asparagi-
nase does not have substantial utility in the treatment of AML, we proposed a study to
the national cooperative group, the Cancer and Leukemia Group B (CALGB), which
compared, by random allocation, the remission induction potential of HiDAC alone vs.
HiDAC with sequential ASNase (Fig. 6). This study included 195 adult patients with
refractory and relapsed AML, all of whom had failed therapy with SDAC, an
anthracycline antibiotic, with and without other drugs. This randomizing study
demонstrated a superior response rate for HiDAC/ASNase compared to HiDAC
alone for patients with refractory AML (Table 4). Response rates for relapsed patients
less than 60 years of age were comparable with the two arms. There was, however, a
higher response frequency from HiDAC/ASNase for relapsed patients over 60 years
of age compared to HiDAC alone [38]. Given these response rates in failed patients,
we were eager to test this in newly diagnosed patients. Results to date indicate that the
complete remission rates in patients with newly diagnosed AML equal those of
ara-C/anthracycline combinations, again suggesting an improvement in response over
standard doses [39]. This finding would suggest that the subsequent inclusion of
another active drug, such as an anthracycline, has the potential for further improve-
ments.

The mechanism of ASNase-potentiation of HiDAC is under exploration in L5178Y
cells. Asparaginase alters the cellular pool size of cytidine triphosphate (CTP) and
dCTP in a schedule-dependent fashion. While we do not have definitive data, our
hypothesis is that the decrease in CTP may be related to the glutaminase effect of
ASNase with lowered glutamine pools and subsequent effect on the activity of CTP
synthetase. The administration of ara-C during this period of lower CTP and dCTP
pools is associated with increased ara-CTP, ara-C DNA, and ara-CDP-choline
synthesis [19]. This area requires further investigation.

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