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Commentary

High-dose Cytosine Arabinoside Therapy in Acute Non-lymphocytic Leukemia

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ATTENTION has recently focused on the use of cytosine arabinoside (araC) in patients with acute non-lymphocytic leukemia (ANLL) at dose levels which are 30-fold higher than that usually employed (3 g/m^2 vs 100–200 mg/m^2 respectively [1–3]. This therapeutic approach is based on the concept that resistance to araC is due to inadequate cellular uptake which can be circumvented by the administration of high dosages. The theoretical basis for this approach is that at low drug concentration levels araC uptake is limited by facilitated diffusion while at high drug levels araC enters cells by passive diffusion [4, 5]. Nevertheless, the question remains as to the role of high dose araC therapy (HDaraC) in the treatment of acute leukemia.

REMISSION INDUCTION THERAPY

While direct comparative trials have not been conducted, there appears to be little question that araC at high doses is more effective than at conventional doses. Early trials of araC in acute nonlymphocytic leukemia (ANLL) employed dose levels between 100 and 200 mg/m^2/day until aplasia was produced (after 20–30 days of therapy), and in repeated 5-day courses to aplasia a remission rate of 15–30% was produced [6–8]. Using a schedule of 3 g/m^2 q. 12 hr for 6 days we achieved a 40% complete remission rate in very high risk previously untreated patients (high risk = >70 yr old, secondary ANLL or inability to receive anthracycline antibiotics) [9]. Capizzi and co-authors [10], using a different HDaraC schedule in standard risk patients, have reported even higher CR rates. Hence as single-agent therapy HDaraC appears to be superior to conventional dose araC therapy.

While HDaraC is superior to conventional dose araC therapy, is it superior to or equivalent to combination chemotherapy? The definitive answer to this question is unknown. We have treated 43 standard risk patients at first relapse with HDaraC and achieved a CR rate of 23%, with 42% of patients failing to enter remission because of persistent leukemia [9]. In a parallel study we achieved a 50% CR rate in comparable patients with conventional-dose araC/anthracycline antibiotic therapy, with only 15% of patients failing therapy because of persistent leukemia [11]. On the other hand, both Hertzig *et al.* [12] and Capizzi *et al.* [10] reported a CR rate of 50% for first relapse patients treated with HDaraC. Therefore no conclusion can be reached at the present time with respect to the efficacy of HDaraC as compared to combination chemotherapy, but our experience suggests that combination chemotherapy is superior.

Information is accruing, on the other hand, that there is a role for HDaraC as remission induction for certain subgroups of patients and as part of combination chemotherapy regimens. We have reported that patients with secondary ANLL appear to respond well to single-agent HDaraC therapy [13] and, in work being prepared for publication, we have achieved 5 out of 5 responses in patients with acute myelofibrosis [14]. HDaraC has been combined with an anthracycline antibiotic [12] or with m-AMSA [15] with an

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apparent increase in the CR rate. An alternative approach to remission induction therapy is to administer conventional dose araC/anthracycline antibiotic therapy and, if after 6 days of therapy the marrow still contains significant numbers of leukemic cells, administer HDaraC on days 8–10 ('augmentation' therapy) [16, 17]. This selective administration of HDaraC to patients who are not likely to respond to a conventional remission induction regimen has doubled the expected CR rate in this subset of patients. Its use in this manner, however, should be restricted to patients who are <60 yr of age. HDaraC as remission induction therapy for 2nd relapse patients produced a 23% CR rate and only a 7% CR rate in 3rd relapse patients [9], suggesting that it is ineffective in patients who have had multiple inductions with conventional dose araC/anthracycline antibiotic therapy.

HDaraC AS PART OF CONSOLIDATION THERAPY

There are reasons to believe that the use of HDaraC may improve the efficacy of consolidation chemotherapy [17]. The high araC plasma levels are translated into cerebral spinal fluid levels which produce substantial antileukemia effects [3, 18]. Hence the use of HDaraC in consolidation therapy may provide prophylaxis therapy to the central nervous system and to other 'sanctuary' sites. HDaraC may also improve the efficacy of consolidation therapy since in some cases it is not cross-resistant with conventional dose araC/anthracycline therapy. An additional theoretical advantage of HDaraC in this setting results from the possibility that when the leukemic cell burden is low many leukemic cells may be in cycle, rendering them especially sensitive to an S-phase-specific agent. There are significant theoretical advantages to alternating courses of HDaraC/AMSA with conventional-dose araC/anthracycline antibiotics since this approach may delay or prevent the outgrowth of resistant cells [19].

TOXICITY

HDaraC remission induction therapy produces hematopoietic toxicity, which in standard risk patients is comparable to that produced by conventional-dose combination chemotherapy. The hematopoietic toxicity, however, may be less than conventional chemotherapy for patients with secondary ANLL [13]. The severe conjunctivitis produced by HDaraC therapy is preventable by the prophylactic use of steroid containing eye drops [20]. Cerebellar toxicity ranging from a barely detectable tremor to a severe, irreversible pancerebellar syndrome is the most distressing toxicity. While the irreversible pancerebellar syndrome is uncommon, some degree of cerebellar toxicity can be detected in 10–15% of patients treated with a 6-day course of therapy [21]. Patients at especially high risk are the elderly, individuals who have received prior central nervous system therapy with radiation or perhaps methotrexate, and alcoholics. Recently cerebellar toxicity has appeared in patients receiving a 2nd or 3rd course of HDaraC [22]. This observation suggests the possibility of cumulative neurologic toxicity, which may be akin to the cumulative effects of the anthracycline antibiotics on the myocardium. Patients who have recovered from an episode of severe cerebellar toxicity may experience a recurrence when treated with araC at conventional dose levels. Other possible neurologic complications include reversible short-term memory loss and perhaps, on rare occasions, peripheral neuropathy.

A severe respiratory distress syndrome has been associated with HDaraC administered by continuous or near-continuous infusion [23, 24]. Other toxicities include liver function abnormalities, hyperpigmentation of the skin, rashes and hair loss.

RATIONAL CHEMOTHERAPY

Perhaps the most significant potential benefit derived from the introduction of HDaraC therapy is the possibility of its use in therapy tailored to the needs of the individual patient. There is evidence that some patients with ANLL will do extremely well for many years receiving single-agent araC therapy [25]. Identification of these patients at the time of diagnosis would permit administration of an effective therapy which produces less toxicity than do the combination chemotherapies currently in use. Similarly, a large proportion of patients (≥40%) will enter CR with a single course of HDaraC therapy. The ability to identify these patients would simplify therapy for these individuals.

AraC is an S-phase-specific agent which probably must be incorporated into DNA for cells to be killed [26, 27]. The incorporation of araC into DNA is associated with the inhibition of DNA synthesis. The Intergroup leukemia study has evaluated several potential methods for predicting response to HDaraC therapy [9]. We have found that there are 3 basic mechanisms of resistance to this therapy [28]: a high pretherapy tumor cell mass as indicated by a high bone marrow biopsy cellularity; resistance because few cells are in S phase (cell cycle resistance); and metabolic resistance indicated by an inability of araC to inhibit leukemic cell DNA synthesis. Each of these is an independent determinant of

response and studies currently in progress suggest that simultaneous assessment of all 3 parameters would permit the recognition of virtually all patients who will fail to enter CR because of persistent leukemia [9]. Our initial pharmacokinetic studies suggest that treatment failure due to low plasma araC levels is uncommon when HDaraC is administered but that induction death may be associated with high plasma araC levels [9].

While HDaraC therapy appears to be a useful addition to the therapeutic armamentarium, the optimal dose and schedule of administration is not known. Two schedules are currently in use. In one, araC is administered at 3 g/m^2 q. 12 hr as a 3-hr infusion for 2 days followed by L-asparaginase, a 1-week rest period, and another 2-day course of araC and L-asparaginase [10]. The second schedule is 3 g/m^2 q. 12 hr as a 75-min infusion × 6 days [2, 3, 12]. A direct comparison of these two regimens has not been carried out. We have begun to use a preparative regimen for autografting of patients in blastic crisis of CML consisting of araC 3 g/m^2 q. 12 hr × 3 days followed by a 1-week rest and 3 additional days of HDaraC therapy. To date 3 out of 4 patients have entered a 2nd chronic phase with little difficulty. Clearly, further studies of HDaraC scheduling are necessary. A potential advantage of the split course of araC therapy may be a lesser degree of cerebellar toxicity than when a 6-day course of therapy is administered and the possible recruitment of non-cycling cells into cycle, thus rendering them sensitive to the second 2 or 3 days of araC therapy.

A second question relates to the optimal dose level. While there have not been comparative studies of 2 vs 3 g/m^2, we have administered 2 g/m^2 to 15 patients $\geq$70 yr old with a 40% CR rate, a CR rate which is identical to that produced in 50 previously untreated patients treated with 3 g/m^2. If these observations reflect the relative efficacy of araC at these two dose levels, perhaps the incidence of the CNS toxicity of HDaraC could be reduced by using the lower dose level without compromising therapeutic efficacy. One must be cautious, however, about generalizing from these observations since metabolic resistance to araC becomes more common as the number of relapses increases [unpublished observations].

Future studies should be directed towards the more selective use of chemotherapy. The data presented in this issue [5] and elsewhere [4, 20] suggest that the shape of the dose–response curve to araC varies significantly between patients and that some patients might benefit equally from conventional-dose or even 'low-dose' araC therapy [30]. On the other hand, patients who are likely to fail HDaraC therapy because few cells are in S-phase are ideal candidates to test the efficacy of regimens designed to recruit cells into the cycle since these could be followed by HDaraC therapy. Finally, patients with a high pretherapy tumor cell mass or in whom the day 6 bone marrow aspirate contains >40% abnormal cells may benefit from the addition of another agent to the HDaraC regimen [9]. By using these criteria, the addition of other agents to patients being treated with HDaraC could be restricted to those individuals who are likely to fail HDaraC therapy because of persistent leukemia, thereby limiting the possible increased risk of severe toxicity to those patients for whom the risk may be worthwhile.

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