

## Sense and nonsense of high-dose cytarabine for acute myeloid leukemia

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**High-dose cytarabine applied during remission induction or as consolidation after attainment of a complete remission has become an established element in the treatment of adults with acute myeloid leukemia. Recent evidence has challenged the need for these exceptionally high-dose levels of cytarabine. In this review, we present a reappraisal of the usefulness of high-dose cytarabine for acute myeloid leukemia treatment. (*Blood*. 2013;121(1):26-28)**

### Early studies that have established the use of HDAC in first-line treatment

Cytarabine is one of the major drugs in the treatment of acute myeloid leukemia (AML) since more than 3 decennia. Originally, the drug has been used in standard schedules at 100-200 mg/m<sup>2</sup> for 7-10 days (so-called “conventional-dose” cytarabine).<sup>1</sup> Around 1975-1985, investigators began to pioneer high-dose cytarabine (HDAC) at 3000 mg/m<sup>2</sup> twice daily for 6 days. In single-arm studies, positive response rates were noted in relapsed patients and encouraging results were also seen in newly diagnosed patients.<sup>2-4</sup> These studies were uncontrolled and involved limited numbers of patients. In a 3-arm randomized study conducted by the Cancer and Leukemia Group B (CALGB) leukemia study group in 596 patients 15-86 years of age, 4 cycles of HDAC at 3000 mg/m<sup>2</sup> twice daily (on 3 days) applied for consolidation after attainment of complete remission were compared with 4 cycles of cytarabine at 400 mg/m<sup>2</sup> and 4 cycles at 100 mg/m<sup>2</sup>.<sup>5</sup> The HDAC schedule appeared superior as regards overall survival (OS) of randomized patients and disease-free survival (DFS; ie, survival without failure because of relapse or death for the patients in complete remission). The question whether such an enormous dose increase to 3000 mg/m<sup>2</sup> was necessary and if intermediate dose levels of cytarabine with significantly less toxicities might be equally effective remained open. Subsequently, in 2 randomized studies by the Australian and the SWOG cooperative leukemia groups in newly diagnosed adults younger than 60 years, HDAC was compared with cytarabine at conventional-dose levels in induction.<sup>6,7</sup> Both studies demonstrated significantly better DFS for the HDAC treatment group. However, OS was not improved. The first study evaluated HDAC at 3000 mg/m<sup>2</sup> every 12 hours on 4 days in combination with daunorubicin and etoposide during cycles I and II, which was compared with a similar combination of chemotherapy but with cytarabine at 100 mg/m<sup>2</sup> by continuous intravenous infusion for 7 days.<sup>6</sup> There was a better DFS but a higher initial death rate and OS was not improved after the HDAC approach. The second study used HDAC at 2000 mg/m<sup>2</sup> every 12 hours on 6 days (along with daunorubicin) in cycle I, which was compared with 200 mg/m<sup>2</sup> cytarabine given continuously intravenously on days 1-7.<sup>7</sup> There was a second randomization for consolidation with one cycle of HDAC plus daunorubicin versus 2 cycles of conventional-dose cytarabine combined with daunorubicin, but this involved a limited subset of cases only. The latter study demonstrated an improved DFS in favor of HDAC but no improved OS. In all 3 studies, HDAC appeared as a very toxic treatment that is associated with

increased hematologic, neurologic (eg, cerebellar), and organ toxicities (eg, hepatic, gastrointestinal, ocular, skin), and the toxicities prohibited the effective and safe delivery of HDAC in patients older than 50-60 years.<sup>5</sup> After these reports, the use of HDAC in the treatment of AML, especially in patients younger than 60 years, either for remission induction or consolidation has become common practice, but critical questions as regards the therapeutic value of HDAC and particularly regarding the dose-effect relationship remained unresolved. Are these huge dosage increments of HDAC necessary? Or are intermediate-dose levels of cytarabine perhaps equally useful with the advantage of considerably reduced toxicities. Recent large cooperative group study reports have created new light on these questions (Table 1).

### Results from recent studies challenge the dogma of HDAC treatment in AML

Compelling evidence would indicate that HDAC at dose levels of 2000-3000 mg/m<sup>2</sup> are above the plateau of the maximal therapeutic effect. They add serious toxicities without adding demonstrable antileukemic effects. In a Dutch-Belgian-Swiss cooperative study by the HOVON/SAKK cooperative group in 860 patients with newly diagnosed AML between 18-60 years of age, 2 sequential induction cycles I and II with cytarabine at 1000 mg/m<sup>2</sup> every 12 hours (5 days) and 2000 mg/m<sup>2</sup> every 12 hours (4 days) were compared with 2 combination cycles based on cytarabine at 200 mg/m<sup>2</sup> by continuous intravenous infusion for 7 days (cycle I) and 1000 mg/m<sup>2</sup> twice daily for 6 days (cycle II).<sup>8</sup> The study offered a “clean” comparison because cytarabine was not used during other phases of the treatment protocol. The study did not reveal benefits as regards the dose-escalated HDAC regimen for any of the major therapeutic endpoints, including response, DFS, and OS, and indicated that a dose escalation above an intermediate-dose level of 1000 mg/m<sup>2</sup> twice daily is not useful. Furthermore, the dose-escalated cytarabine program added a considerable amount of toxicities (bone marrow, various severe adverse events, prolonged hospitalization, more deaths at 3 months) arguing against the HDAC regimen. A German Study Alliance (SAL) Group cooperative study in 933 patients between 15 and 60 years of age randomized patients between consolidation with a combination of mitoxantrone and HDAC at 3000 mg/m<sup>2</sup> every 12 hours (6 days)

**Table 1. Phase 3 studies concerned with the therapeutic value of dose-escalated cytarabine (HDAC, 2000-3000 mg/m<sup>2</sup>) regimens in AML in adults up to 60 years of age**

	Reference	Study size, n	Improved outcome for HDAC	
			DFS	OS
<b>Remission induction chemotherapy</b>				
HDAC (3000) vs Ara-C 100*	6	301	Yes	No
HDAC (2000) vs Ara-C 200*	7	665	Yes	No
HDAC 1000/2000 vs Ara-C 200/1000*	8	840	No	No
<b>Consolidation of complete remission</b>				
HDAC (3000) vs Ara-C 100/400†	5	596	Yes	Yes
HDAC (3000) vs Ara-C 1000*	9	933	No	No
HDAC (2000) vs Ara-C 200*	10	781	No	No

HDAC indicates high-dose cytarabine at 2000 mg/m<sup>2</sup> or 3000 mg/m<sup>2</sup> per intravenous infusion given twice daily; and Ara-C, cytarabine at conventional dose (100, 200, 400 mg/m<sup>2</sup> per 24-hour continuous infusion) or intermediate dose (1000 mg/m<sup>2</sup> twice daily).

\*In adults younger than 60-65 years.

†In adults 15-86 years of age.

versus a similar chemotherapy program but with cytarabine at 1000 mg/m<sup>2</sup> twice daily for consolidation.<sup>9</sup> The results of the HDAC 3000 mg treatment group were not better for any of the major clinical endpoints. In this respect, it should be noted that during remission induction all patients had already been exposed to an induction cycle of combination chemotherapy that had included cytarabine at 1000 mg/m<sup>2</sup> twice daily during 5 days. Thus, 2 recent studies, one for remission induction and the second one for postremission, failed to show an antileukemic advantage of cytarabine dose intensification > 1000 mg/m<sup>2</sup> twice daily. The Japanese AML group in a third recent study in 781 complete responders (newly diagnosed patients 15-64 years of age) failed to show a benefit for 3 cycles of HDAC (2000 mg/m<sup>2</sup> every 12 hours for 5 days) compared with 4 cycles of a multiagent chemotherapy consolidation program at conventional-dose levels that contained 200 mg/m<sup>2</sup> cytarabine by 24-hour continuous infusion for 5 days.<sup>10</sup> The investigators of each of these recent studies also addressed the potential issue of allogeneic stem cell transplantation that was applied as postremission treatment in a subset of their patients in their studies. They confirmed the lack of a benefit of HDAC after they had checked for interaction with allogeneic stem cell transplantation or censored for allogeneic stem cell transplantation.

### Any value of HDAC for specific subsets of AML?

A retrospective analysis from the CALGB study group<sup>11</sup> that was reported several years after the appearance of their original publication<sup>5</sup> showed that the survival advantage of HDAC at 3000 mg/m<sup>2</sup> twice daily compared with standard-dose 100 mg/m<sup>2</sup> and 400 mg/m<sup>2</sup> cytarabine was predominantly apparent in patients with favorable risk cytogenetics (ie, those with core binding factor [CBF] AML). CBF refers to AML with translocations t(8;21) and inv(16) or t(16;16). The conclusions about a therapeutic advantage of HDAC in these subtypes of AML had been derived from a subgroup analysis in 57 patients with CBF AML who altogether had been assigned to the 3 cytarabine dose treatment groups; thus, the analysis is based on very small numbers.<sup>11</sup> The investigators also suggested that patients with AML with *RAS* gene mutations are the ones who benefit from dose escalation, but the total numbers of

34 cases distributed over 3 study arms on which this analysis is based are again very small.<sup>12</sup> A Japanese study confirmed that CBF AML (n = 218 cases) benefit from HDAC treatment (2000 mg/m<sup>2</sup>) at least when HDAC is compared with conventional-dose (200 mg/m<sup>2</sup>) cytarabine.<sup>10</sup> These authors reported a DFS benefit, no OS advantage. Thus, HDAC treatment for CBF favorable risk AML appears superior to conventional-dose cytarabine (at 100-400 mg/m<sup>2</sup>). But what about the value of HDAC compared with intermediate-dose cytarabine? The recent studies from the HOVON/SAKK and SAL groups<sup>8,9</sup> concur that escalation of cytarabine dose above a threshold of 1000 mg/m<sup>2</sup> is not needed for patients with CBF AML subtypes either. In these large 2-arm phase 3 studies, dose intensification of cytarabine > 1000 mg/m<sup>2</sup> did not impact on improving survival in the subgroups of 88 patients with CBF AML<sup>8</sup> and 272 cases of CBF AML.<sup>9</sup>

### How many cycles of HDAC?

The German AML Cooperative Group study group compared in a double induction strategy 2 induction cycles of combination chemotherapy of HDAC (3000 mg/m<sup>2</sup> every 12 hours on days 1-3) with 2 induction cycles of which only one contained a HDAC schedule and the other cycle contained conventional-dose cytarabine.<sup>13</sup> They failed to demonstrate an improvement in relapse probability, DFS, or OS after 2 HDAC cycles. These results are consistent with the notion that one cycle of HDAC would be enough if HDAC was effective at all. The Australian AML group randomized 202 patients in complete remission (15-60 years) and reported a lack of any added therapeutic value of consolidation with 3000 mg/m<sup>2</sup> HDAC that followed remission induction with a HDAC regimen of 3000 mg/m<sup>2</sup> every 12 hours on days 1, 3, 5, and 7 with anthracyclines. Thus, they reaffirmed that more than one cycle of HDAC was redundant.<sup>14</sup> The German SAL group demonstrated that cytarabine 1000 mg/m<sup>2</sup> in induction followed by 1000 mg/m<sup>2</sup> for consolidation is as effective as the same treatment but with 3000 mg/m<sup>2</sup> for consolidation.<sup>9</sup> The CALGB leukemia group in 306 randomized patients (15-59 years) who had been in complete remission after a 7 + 3 induction schedule reported that 3 cycles of HDAC at 3000 mg/m<sup>2</sup> given every 12 hours on days 1, 3, and 5 were not better than 3 cycles of chemotherapy that included only one cycle of HDAC.<sup>15</sup> These studies provide uniform evidence indicating that after a single cycle of HDAC successive cycles of HDAC do not contribute additional measurable therapeutic advantages.

### Conclusions: "Let us stop dropping the big one?"

HDAC at 2000 mg/m<sup>2</sup> or 3000 mg/m<sup>2</sup> has become widely accepted as an important element in the therapeutic management of AML. However, the time has come to question the usefulness of HDAC and perhaps discourage the application of HDAC, even though we should bear in mind that there remain several unknowns. For example, we do not know how much the infusion rate of HDAC matters. In the phase 3 studies that evaluated HDAC, HDAC was applied during variable 1-hour,<sup>7</sup> 3-hour,<sup>5,6,10</sup> or 6-hour<sup>8</sup> infusions, although it was not specified for another study.<sup>9</sup> How important these differences in infusion rates, which will influence peak concentrations of the drug after infusion, are for optimizing therapeutic efficacy, is presently unclear. On the other hand, the

cumulative doses applied during successive cycles and thus total drug exposure might have been important as well. The cumulative doses ranged widely between the studies. In the CALGB study, the cumulative doses of cytarabine between the 3 treatment groups compared 2000 mg versus 8000 mg versus 72 000 mg in the individual patient.<sup>5</sup> The Japanese study that involved multiple cycles of HDAC has dealt with a similar cumulative dose comparison (4000 mg vs 90 000 mg total dose).<sup>10</sup> These doses have been so high because HDAC was administered during repeated cycles of chemotherapy. The total comparative doses of HDAC applied in the SWOG study (1400 mg vs 24 000 mg),<sup>7</sup> the Australian study (1400 mg vs 48 000 mg),<sup>6</sup> the German SAL study (12 000 vs 36 000 mg),<sup>9</sup> and the Dutch-Belgian-Swiss HOVON/SAKK study (15 000 mg vs 26 000 mg total dose)<sup>8</sup> reached lower ceilings of dose accumulation. Finally, we should keep in mind that HDAC was applied in the context of different drug combinations (eg, with etoposide, daunorubicin, amsacrin) and in association with different postremission programs, which in variable ways might have influenced the therapeutic evaluation of HDAC schedules. For instance, the dose intensity of daunorubicin has been established as an important treatment variable.<sup>16,17</sup> In the earlier HDAC phase 3 studies,<sup>5-7</sup> daunorubicin was applied at 45-50 mg/m<sup>2</sup> (for 3 days), which today would probably be regarded as a suboptimal setting for evaluating HDAC,<sup>16,17</sup> and this may perhaps explain why a DFS advantage of HDAC was noted in the early phase 3 studies only. In the recent comparative studies,<sup>8-10</sup> with no apparent superiority of HDAC, higher-dose intensities of anthracyclines have been used.

There is no question that HDAC programs induce a variable spectrum of serious toxicities, including the risk of excess mortality. The use of HDAC may also compromise the application of subsequent treatment because of accumulating or prohibitive toxicities over time. HDAC cannot be effectively and safely delivered to patients of older age. Although the maximally effective dose level of cytarabine in AML has not been defined in precise quantitative dose-effect studies, the results of recent large controlled studies appear remarkably concordant. Although from a therapeutic point HDAC appears superior to conventional 100/200 mg/m<sup>2</sup> dose levels, raising the dose level of cytarabine above the intermediate level of 1000 mg/m<sup>2</sup> twice daily does not appear to make sense. There is no direct evidence either to suggest that any particular genetically defined subset of AML would benefit from HDAC dose levels of the drug. The accumulated circumstantial evidence may even suggest the plausible notion that a single cycle of 1000 mg/m<sup>2</sup> cytarabine given twice daily in the treatment of AML might be sufficient.

## Authorship

Contribution: B.L. wrote the paper.

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