ARTICLE - Acute Myeloid Leukemia

Guadecitabine improved relapse-free survival in high-risk acute myeloid leukemia and myelodysplastic syndrome patients after transplant: phase II results from a single center

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Supplemental Document

Extended Methods

Eligibility criteria

For cohort 1 (hematological relapse), patients were initially eligible if they relapsed at any time point post-transplant, though the protocol was later amened to include only those relapsing after day +90.

For Cohort 2 (MRD-positive), patients had to be in morphological remission but exhibit MRD via multi-color flow cytometry (MFC), cytogenetics or next generation sequencing (MGS). MRD monitoring was routinely conducted at day +30, +100, +180, 18 months and 2 years post-transplant via bone marrow evaluation following departmental guidelines.

Cohort 3 (maintenance) required patients in complete remission (CR) within 100 days post-allo SCT and exhibit high risk features. CR status was confirmed via bone marrow assessment within 28 days of enrollment. Hematological recovery was defined as absolute neutrophil count (ANC) >=$1x10^9$/L and platelets >=$50X10^9$/L without transfusions for 14 days. Resolution of significant transplant-related complications, including GVHD was required.

Treatment protocol details

Guadecitabine was administered subcutaneously for 5 consecutive days per 28-day cycle. In cohotst 1 and 2, the initial dose was 40 mg/m2/day, later increased to 60 mg/m2/day in cohort 1. A mazimum of 6 cycles were given unless disease response allowed continuation at reduced dose (up tp 12 cycles). In cohort 3, patients received 30 mg/m2 for 12 total cycles.

DLI was administered in cohorts 1 and 2. Up to three DLI infusions were allowed, administered on day 6 of guadecitabine cycles 2, 4, 6. Contraindications included active GVHD or donor chimerism <5%. Patients receiving DLI were required to be off systemic steroids. Calcineurin inhibitors were allowed throughout the treatment.

Guadecitabine dose modifications

A. Hematologic Toxicity

- For cohort 1, there was no dose reductions, delays or modifications required for hematologic toxicities during the treatment cycles given with an intent to achieve CR. For patients who achieved CR on study, they received the subsequent cycles (given as maintenance therapy) approximately every 28 days, provided that their peripheral blood counts recovered (ANC>=1.0 X 10^9 /L and platelet count>=50 X 10^9 /L)). If the peripheral count recovery was delayed beyond 42 days from Day 1 of the prior cycle and the delay was presumed to be secondary to therapy (after confirmation of achieving morphological remission), the guadecitabine dose might be reduced at least by one level for subsequent doses (e.g. from 40 to 30 mg).
- For cohort 2, there was no dose reductions, delays or modifications required for hematologic toxicities during the treatment cycles given in the continuous presence of MRD.

After the documentation of MRD negative status with the guadecitabine treatment, if the peripheral count recovery was delayed beyond 42 days from Day 1 of the prior cycle and the delay was presumed to be secondary to therapy, the guadecitabine doses might be reduced at least by one level for subsequent doses (e.g., from 30 to 20 mg).

- In cohort 3, ANC and platelet counts were required to be ≥1 × 10^9/L and ≥50 × 10^9/L, respectively, prior to each cycle.

For cohort 3, if the peripheral count recovery was delayed beyond 42 days from Day 1 of the prior cycle and the delay is presumed to be secondary to therapy, the guadecitabine doses might be reduced at least by one level for subsequent doses (e.g., from 30 to 20 mg).

B. Non-hematological toxicity

The dose of guadectiabine was reduced by one level for grade 3-4 reversible toxicities attributable to the drug independent of the disease status at the time of ongoing treatment. If toxicity was still present on next cycle with one dose level reduction, dose was reduced with one more level again (minimum dose is 20 mg/m2 given for 3 subsequent days). If toxicity was present after 2 dose level reductions, guadecitabine treatment was discontinued.

Dose reduction for grade 2 reversible toxicities and other dose modifications was implemented if in the best interest of the patient, after discussion with the primary investigator.

Patients with uncontrolled GVHD while receiving treatment with guadecitabine were not allowed to receive subsequent cycles of guadecitabine until the GVHD was resolved. Systemic steroids as first line GVHD treatment were allowed while on trial, but second line agents were not. Patients who did not achieve resolution of GVHD within 70 days after the previous cycle, were removed from the trial. If GVHD resolved, patients might receive guadecitabine with at least one level dose reduction in the subsequent cycle. If GVHD remained controlled, full dose could be used in the subsequent cycles.

Guadecitabine dose levels:

20 mg/m^2 SC	Days 1 through 3	Dose level -3
20 mg/m^2 SC	Days 1 through 5	Dose level -2
30 mg/m^2 SC	Days 1 through 5	Dose level -1
40 mg/m^2 SC	Days 1 through 5	Dose level 1
50 mg/m^2 SC	Days 1 through 5	Dose level 2
60 mg/m^2 SC	Days 1 through 5	Dose level 3

Response assessment

Response in cohort 1 was based on morphological complete remission using International Working Group criteria. MRD negativity in cohort 2 was confirmed by repeat MFC, cytogenetics or molecular studies. Bone marrow evaluations were performed at enrollment and following cycles 2, 4 and 6.

For Cohort 3, MRD and disease status assessments were conducted on day +100, +180, 1 year, 18 months and 2 years after allogeneic stem cell transplant.

Statistical Design

The same phase IIA design was used for cohort 1 and 2, as follows: A response probability of .20 or greater was considered promising. A maximum of 25 patients were planned to be treated in each group, with the probability of response monitored using the Bayesian method of Thall and Dimon. Accrual was to be stopped for futility if fewer than or equal to 0/8 or 1/20 responses were observed. Any patient who started therapy and later permanently discontinued treatment for one of the following reasons was considered a treatment failure (i.e., a non-responder: 1) progressive disease, or 2) death, or 3) dropout, or 4) physician determination that continuation was futile or 5) severe

toxicity prior to achieving disease remission. Patients who did not complete the first cycle of treatment were considered non-evaluable.

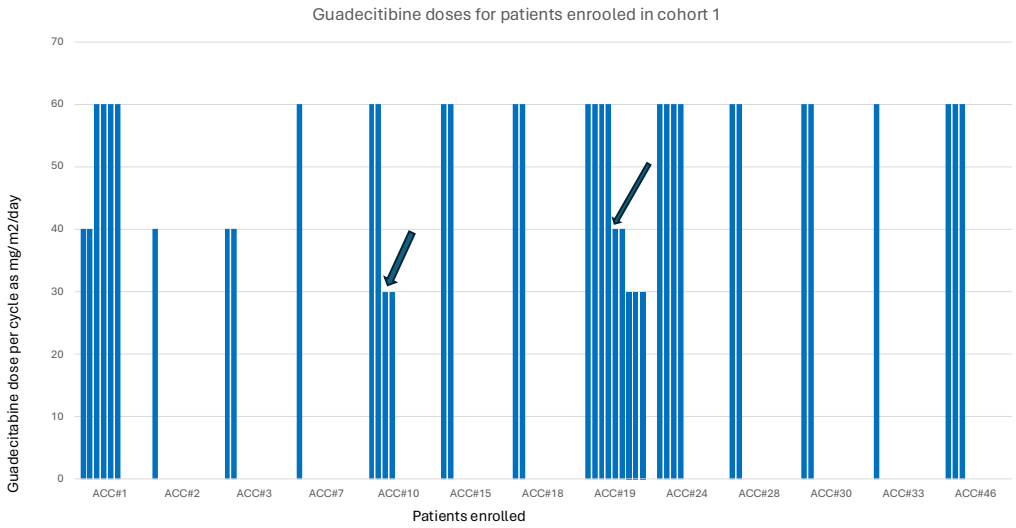
Cohort 3, the maintenance cohort, included high risk patients with one-year relapse incidence of 35%-45%. A maximum of 40 patients were planned to be enrolled. The Bayesian method of Thall et was used to monitor RFS time for futility in this cohort.

Extended Results

Guadecitabine dosing during the trial

In cohort 1, which included patients with relapsed disease, we initially recommended starting the guadecitibine at 40 mg/m^2/day for 5 consecutive days, with a maximum of 6 cycles for remission to achieve remission. However, after no response was observed in the first 3 patients enrolled, the dose was amended as 60 mg/m^2/day. Patients removed from the trial if they did not achieve response within 6 cycles of treatment. Patients who achieved remission were recommended to reduce the dose at least 1 level, preferably 2 levels (dose levels were summarized in the supplementary material).

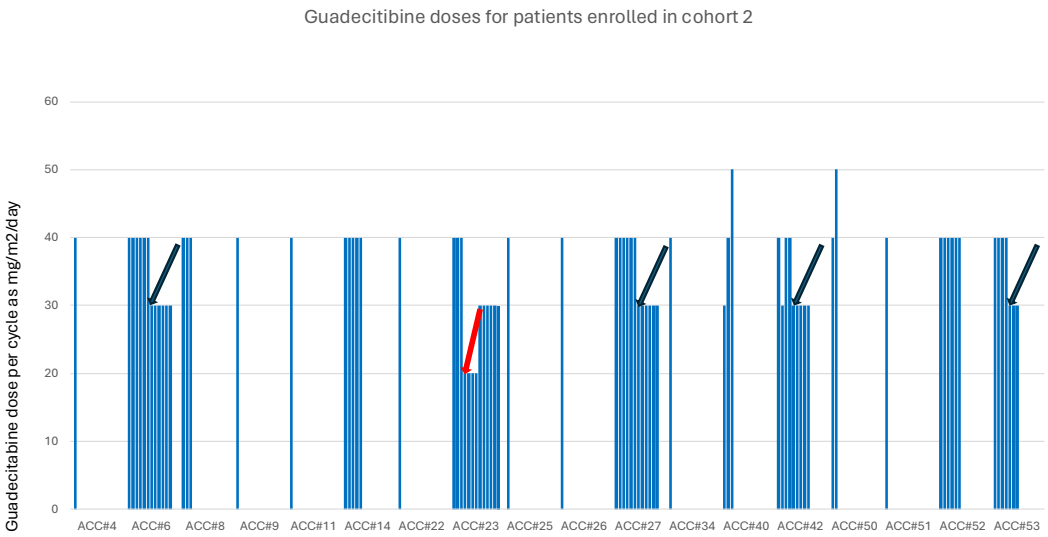
As seen in the graph below, 10 patients started the treatment at the recommended dose of 60 mg/m^2/day but 3 received as 40 mg/m^2/day. Dose reduction was implemented in 2 patients who continued treatment after achieving complete remission.



*The arrow indicates dose reduction recommended per protocol after patients were documented to achieve remission.
Each line per patients indicated one cycle of treatment.

In cohort 2, which included patients with MRD after allo-SCT, we initially recommended starting the guadecitibine at 40 mg/m^2/day for 5 consecutive days, with a maximum of 6 cycles to achieve remission defined as MRD eradication. The dose level of guadecitabine could be increased at least one dose level at the discretion of treating physician. Dose reductions were recommended for patients achieving MRD eradication and/or patients with toxicity observed.

As seen below, 17 of 18 patients started treatment at the recommended dose of guadecitibine at 40 mg/m^2/day for 5 consecutive days. Two patients had dose increase due to not responding to recommended dose of guadecitabine at the discretion of their treating physician.



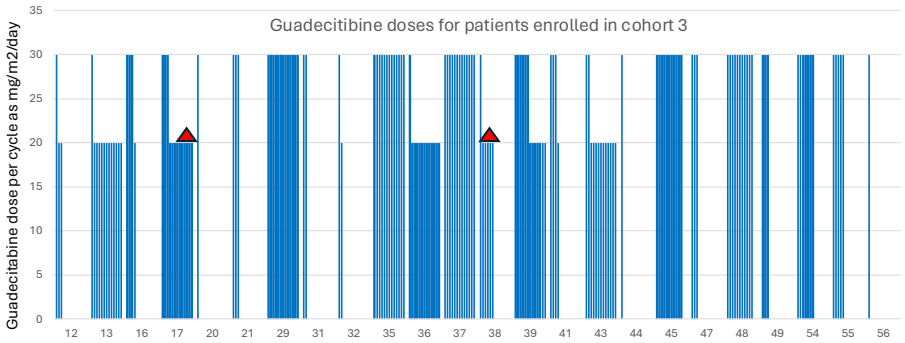
*The black arrow indicates dose reduction recommended per protocol after patients were documented to achieve remission . Red arrow indicated dose reduction both due to achieving remission and observed toxicity.

Each line per patients indicated one cycle of treatment.

For cohort 3, maintenance cohort, enrolled patients started treatment at the dose level -1 which was 30 mg/m2 SC daily, days 1 to 5 for each 28-day

Dose reduction was recommended in cases of hematologic and non-hematologic toxicity.

As shown in the below graph, 10 patients of 24 patients required dose reduction due to toxicity observed during the trial and continued their treatment with guadecitabine at 20 mg/m^2/day for 5 days dose. Two patients required further dose reduction and continued treatment with guadecitabine at 20 mg/m2/day for 3 days per cycle.



Red triangle indicates that patients received guadecitabine at 20 mg/m2/day dose but for 3 consecutive days rather than 5 consecutive days.

Each line per patients indicated one cycle of treatment.