A phase 1 trial of vadastuximab talirine combined with hypomethylating agents in patients with CD33-positive AML

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Introduction

Outcomes for patients with acute myeloid leukemia (AML) remain poor, particularly in older patients, who are more likely to have adverse disease features and may not be candidates for aggressive induction and consolidative approaches including stem cell transplant.1-3 Hypomethylating agents (HMAs), decitabine or 5-azacitidine, are now increasingly used in this population as lower-intensity therapy, but are associated with low rates of remission.4,5 The development of novel, well-tolerated therapies to enhance the efficacy of HMAs could meaningfully improve the standard of care for older patients with AML.

CD33, or Siglec-3, is a transmembrane receptor expressed on leukemic blasts in the majority of cases of AML, and is therefore an ideal target for novel therapeutic approaches. Several antibody-based therapies targeting CD33 have been developed and studied in clinical trials. Lintuzumab, an immunoglobulin G1 humanized antibody, was well-tolerated in early-phase studies, but demonstrated limited activity as a single agent and was ineffective when combined with conventional therapies.7-9 Gemtuzumab ozogamicin (GO), an antibody–drug conjugate (ADC) bound to the cytotoxic compound calicheamicin, attained accelerated approval by the US Food and Drug Administration in 2000, based on promising monotherapy data in relapsed/refractory
Materials and methods

Patient eligibility

Eligible patients had a new diagnosis of CD33-expressing AML, as determined by local laboratory assessment by flow cytometry. They could not have received prior therapy with HMAs; however, prior low-intensity treatment, such as hydroxyurea for cyto-reduction or other low-intensity therapies for preceding myelodysplastic syndrome (MDS), were allowed. Patients were aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, with adequate baseline renal, hepatic, and pulmonary function. Those with central nervous system leukemia were ineligible.

Study design and treatment

The combination portion of this phase 1 study (NCT01902329) was designed to evaluate the safety, tolerability, pharmacokinetics (PK), and antileukemic activity of vadastuximab talirine when administered in combination with either azacitidine or decitabine. Fourteen centers in the United States recruited patients between July 31, 2013, and February 17, 2016, under approval by an Institutional Review Board in accordance with the Declaration of Helsinki. All patients provided informed consent before administration of any study treatment.

Azacitidine (75 mg/m² subcutaneous/intravenous × 7 days) or decitabine (20 mg/m² intravenous × 5 days) was administered per institutional standard. On the final day of HMA administration (day 7 of azacitidine treatment and day 5 of decitabine treatment), vadastuximab talirine was administered via slow intravenous push (1-2 mL/min), after infusion of the HMA. The dose of vadastuximab talirine was 10 μg/kg, the recommended combination dose determined by the safety monitoring committee based on the monotherapy dose escalation portion of the study. This HMA combination treatment was repeated as 28-day cycles for up to 4 cycles of treatment. Patients who achieved clinical benefit during the first 4 cycles were eligible for extension treatment every 28 days at either 10 μg/kg (as before, in combination with HMA) or a lower dose of 5 μg/kg. Extension treatment was allowed in the absence of new or cumulative, clinically significant toxicity and in the absence of relapsed disease.

The evaluation period to assess for dose-limiting toxicity (DLT) was the first cycle of treatment. A DLT was defined as any clinically significant, nonhematologic adverse event (AE) grade 3 or above according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 4.03, or a hypocalcemia (≥5% cellularity) or aplastic bone marrow without evidence of leukemia that lasted more than 28 days from first observation. Febrile neutropenia that resolved with appropriate treatment or marrow recovery was not considered a DLT.

End-of-treatment assessments were conducted approximately 30 days after receiving the final dose of study drug, or within 7 days of documentation of the patient’s decision to discontinue treatment, whichever was later. Patients who discontinued treatment before disease progression were followed for response assessments. All patients were followed monthly for survival.

Study assessments

Safety assessments

Safety assessments included documentation of AEs, vital signs, clinical laboratory tests, ECOG performance status, and physical examination. Grade and term of AEs were reported by the treating physician. Treatment-emergent AEs (TEAEs) were defined as any AE that was newly occurring (not present at baseline) or worsening in severity after initiation of study drug treatment. Complete blood counts and serum chemistries were obtained weekly during the first 4 cycles for all patients; laboratory surveillance was less frequent during extension treatment. Pulmonary function tests, including diffusing capacity of the lung for carbon monoxide, were measured during the first and second cycles and after every 2 cycles subsequently.

Response/efficacy assessment

Antileukemic activity was assessed by routine laboratory tests (complete blood counts) and bone marrow examinations, including flow cytometry evaluation for residual leukemic blasts. Response categorization was based on the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Bone marrow examinations were performed at baseline (within 28 days of starting treatment),...
after cycle 1 and cycle 2, after every other cycle until remission, and then every 4 cycles thereafter, for response assessment, and as surveillance of marrow recovery. Minimal residual disease (MRD) was assessed by 10-color multiparameter flow cytometry\(^{20}\) at a central laboratory during protocol-specified response assessment points: if a marrow biopsy was performed during other cycles of therapy, local flow cytometry results were collected and used for assessment.

**Pharmacokinetic, pharmacodynamic, and immunogenicity assessments** Sensitive, qualified assays were used to measure concentrations of ADC (vadastuximab talirine), total antibody (TAb), and released free drug, SGD-1882, in plasma, as well as antitherapeutic antibodies in serum. The assays included enzyme-linked immunosorbent assays and liquid chromatography-tandem mass spectrometry assays. PK parameters were estimated by noncompartmental analysis using Phoenix WinNonlin v6.3 (Certara, Princeton, NJ).

**Statistical analysis** The primary objective was to evaluate the safety and tolerability of treatment with vadastuximab talirine when given in combination with azacitidine or decitabine in patients with CD33-positive AML. End points included the type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities, complete remission (CR) rate, overall survival (OS), relapse-free survival, and incidence of DLT.

Study measures of safety, PK, and efficacy were summarized by descriptive statistics. The analysis set for all treated patients included those treated with any amount of vadastuximab talirine. The DLT-evaluable analysis set included all treated patients who either experienced a DLT or were followed for the full DLT evaluation period. The efficacy-evaluable analysis set included all treated patients who received study treatment and had a postbaseline bone marrow examination and response determination. Additional analyses to summarize the time to neutrophil and platelet count recovery were performed. Time to count recovery was calculated from the first dose of study drug to the earliest date that neutrophil count was 1000 units/\(\mu\)L or higher and platelet count was 100 000 units/\(\mu\)L or higher, respectively. Patients whose neutrophil or platelet count did not recover were censored at the last complete blood count date before the data cutoff or start of subsequent therapy, whichever came first.

**Results**

**Patients** A total of 53 patients with AML were treated in the combination portion of the study. The median age was 75 years (range, 60-87 years); most patients had intermediate (62%) or adverse (38%) risk by Medical Research Council (MRC) classification\(^{21}\); the majority of patients (79%) entered the study with an ECOG performance status of 1. Four patients (8%) had received prior non-intensive, non-HMA therapy for MDS. Forty-five percent of patients had secondary AML (defined as AML arising from prior MDS, therapy-related AML, or apparently de novo AML with MDS-related cytogenetics), and 5 patients (9%) harbored a fms-like tyrosine kinase 3 (FLT3)/internal tandem duplication (ITD) mutation. Additional demographic and disease characteristics are presented in Table 1.

**PK** Concentration-time profiles for cycle 1 of vadastuximab talirine ADC, combined with either azacitidine or decitabine, are shown in Figure 1. Serum pyrrolobenzodiazepine concentrations were below the lower limit of quantitation (LLOQ) for all subjects evaluated (LLOQ = 60 pg/mL). Vadastuximab talirine ADC PK was similar when administered with HMA, azacitidine, or decitabine. The ratio of cycle 1 vadastuximab talirine ADC to TAb concentration for all subjects in this analysis was calculated and is shown across time in Figure 2. The mean ADC/TAb ratio

![Figure 1. Mean vadastuximab talirine ADC plasma concentration-time profiles.](https://ashpublications.org/blood/article-pdf/132/11/1125/1372729/blood841171.pdf)

### Table 1. Demographics and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>All treated (N = 53)</th>
<th>Secondary AML (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, y (range)</strong></td>
<td>75 (60-87)</td>
<td>77 (60-87)</td>
</tr>
<tr>
<td><strong>Sex, male, %</strong></td>
<td>64</td>
<td>75</td>
</tr>
<tr>
<td><strong>ECOG, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>88</td>
</tr>
<tr>
<td><strong>MRC cytogenetic risk, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>62</td>
<td>25</td>
</tr>
<tr>
<td>Adverse</td>
<td>38</td>
<td>75</td>
</tr>
<tr>
<td><strong>Underlying myelodysplasia, %</strong></td>
<td>43</td>
<td>54</td>
</tr>
<tr>
<td><strong>Baseline BM blast, %, median (range)</strong></td>
<td>52.5 (20-90)</td>
<td>34 (20-90)</td>
</tr>
<tr>
<td><strong>Baseline WBC ×10^9/(\mu)L, median (range)</strong></td>
<td>2.1 (0.4-132)</td>
<td>1.5 (0.8-18.9)</td>
</tr>
</tbody>
</table>

BM, bone marrow; WBC, white blood count.
approximated 1.0, indicating the majority of the TAb concentration is circulating as ADC. This value remained stable for up to 24 hours postdose, consistent with a stable linker.

The mean concentration-time profiles shown in Figure 1 demonstrate that vadastuximab talirine ADC exhibits rapid elimination, with ADC concentrations for all patients included in this analysis being below the LLOQ (5 ng/mL) at 7 days postdose. When administered in combination with an HMA (azacitidine or decitabine), the vadastuximab talirine ADC concentration-time profile was similar to that seen with monotherapy.\textsuperscript{17} Vadastuximab talirine PK appears to be mainly target-mediated\textsuperscript{22}; therefore, the PK profile reflects the level of target. Within the context of the first cycle, treatment with either HMA does not appear to affect vadastuximab talirine PK (Figure 1), indicating that azacitidine and decitabine have a similar effect on the target during the first week of treatment before vadastuximab talirine administration.

**Safety**

The 30- and 60-day mortality rates were 2% and 8%, respectively. No DLTs or infusion-related reactions were observed in the combination cohort of this study. The majority of TEAEs observed in all treated patients were consistent with myelosuppression; no grade 3/4 nonhematologic TEAEs were observed in 20% or more of patients. TEAEs, regardless of grade, observed in at least 20% of all treated patients are listed in Table 2.

Thirty-three patients (62%) experienced a TEAE of thrombocytopenia, with 57% of all patients experiencing grade 3 or higher thrombocytopenia. Although thrombocytopenia with associated minor bleeding was frequently observed, no serious bleeding events grade 3 or higher were observed. The most frequently reported bleeding events were epistaxis (19%), contusion (11%), and petechiae (11%). Infection of any grade was observed in 79% of patients. The most common grade 3 or higher infections were lung infections (including the terms “pneumonia,” “lung infection,” “pneumonia fungal,” and “pneumonia bacterial,” totaling 34%), sepsis (11%), and bacteremia (11%). Febrile neutropenia was the most commonly reported serious AE (vadastuximab talirine + azacitidine, 23%; vadastuximab talirine + decitabine, 59%). In the limited number of patients treated, the overall safety profile was similar for patients treated with vadastuximab talirine in combination with azacitidine vs decitabine (with the exception of incidence of febrile neutropenia).

Patients received treatment of a median of 19.3 weeks (range, 2-114 weeks) with a median of 3 cycles (range, 1-18 cycles). For patients with active leukemia, the protocol allowed for uninterrupted dosing despite cytopenias; adequate count recovery was only required before subsequent dosing for patients in CR or CR with incomplete blood count recovery (CRi), and thus dose delays primarily occurred in patients who had achieved remission. Forty-three percent of all doses (121/282) were delayed because of an AE, most commonly neutropenia (23%), thrombocytopenia (6%), febrile neutropenia (4%), and anemia (2%). Fourteen patients (26%) discontinued treatment because of any event. The median time to neutrophil count recovery to 1000 units/µL or more for patients who achieved either CR or CRi was 10.6 weeks (95% confidence interval [CI], 6.6-11.9 weeks), and the mean time to platelet recovery to at least 100 000 units/µL was 10.1 weeks (95% CI, 6.1-14.1 weeks), as depicted in Figure 3.

### Table 2. Treatment-emergent adverse events occurring in 20% or more of all treated patients

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Total TEAEs,* n (%)</th>
<th>TEAEs ≥ grade 3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>53 (100)</td>
<td>52 (98)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (62)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>33 (62)</td>
<td>30 (57)</td>
</tr>
<tr>
<td>Nausea</td>
<td>28 (53)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>26 (49)</td>
<td>24 (45)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>26 (49)</td>
<td>26 (49)</td>
</tr>
<tr>
<td>Constipation</td>
<td>25 (47)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>24 (45)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24 (45)</td>
<td>22 (42)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>22 (42)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18 (34)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17 (32)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (28)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (28)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (28)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>13 (25)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (21)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 (21)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Only TEAEs with any grade prevalence of ≥ 20% are included.

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**Figure 2.** Mean vadastuximab talirine ADC:TAb ratio. The mean ADC/Tab ratio approximated 1.0 and remained stable for at least 24 hours postdose. Tab, total antibody.
Blood®

Discussion

Vadastuximab talirine demonstrated potent antileukemic activity across multiple dose levels in the monotherapy dose escalation portion of the phase 1, first-in-human trial conducted primarily in patients with relapsed and refractory AML. The expansion cohort reported here was then conducted to explore its safety, tolerability, and activity in combination with HMAs in older patients with previously untreated AML. Biologic features that correspond to poor response to standard induction chemotherapy are overrepresented in older patients with AML. In addition, age and comorbidities preclude the usage of intensive chemotherapy in many of these patients, and thus HMAs are often considered standard of care. The current study demonstrated that high CRc rates were achievable with the combination of HMAs and vadastuximab talirine, including among traditionally poor-risk subsets of patients, such as those with adverse risk cytogenetics, secondary AML, tumor protein 53 (TP53) mutations, and FLT3/ITD mutations. As previously published, baseline CD33 expression level did not correlate with the likelihood of achieving response or MRD negativity on this phase 1 trial; responses were observed across the spectrum of CD33 expression.

Individual patients

Figure 4. Postbaseline bone marrow blast reduction. Maximum posttreatment percentage change in marrow blasts (relative to baseline), patients who achieved remission are denoted. 10+ Aza = 10 μg/kg vadastuximab talirine plus azacitidine, 10+Dec = 10 μg/kg vadastuximab talirine plus decitabine.

Figure 3. Summary of count recovery. Time to platelet count ≥ 100,000 units/μL and neutrophils ≥ 1000 units/μL is shown for patients who achieved a CR or CRi. NEUT, neutrophils; PLAT, platelets.

Hepatic events

The most commonly reported hepatic AEs of any grade were increased bilirubin (9%), increased alanine aminotransferase (8%), increased aspartate aminotransferase (8%), hyperbilirubinemia (6%), acute/cholecystitis (2%), hepatic cyst (2%), and abnormal hepatic function (2%). No cases of sinusoidal obstructive syndrome/veno-occlusive disease were observed, including in the 2 patients who went on to receive subsequent allogeneic hematopoietic stem cell transplants after completing study treatment.

Efficacy

The composite CR rate (CRc) among all 53 patients in the combination cohort, defined as the sum of CR and CRi, was 70% (43% CR + 26% CRi; 95% CI, 55.7%-81.7%), with 74% achieving blast clearance (CR + CRi + morphologic leukemia-free state [mLFS]; Figure 4; Table 3). The CRc rate for efficacy-evaluable patients was 76% (47% CR + 29% CRi, 95% CI, 61.1%-86.7%), with 80% achieving blast clearance (CR + CRi + mLFS). Median time to remission was 2 cycles (range, 1-8 cycles).

Of the 23 patients who achieved a best response of CR, 57% achieved an MRD-negative response by 10-color flow cytometry, and 43% of the 14 patients who achieved a best response of CRi achieved MRD negativity by flow cytometry.

Similar activity was observed in subsets of high-risk populations such as patients with secondary AML, older patients (age ≥ 75 years), and patients with adverse cytogenetic risk by MRC (Table 3). Among the 24 patients with secondary AML, the CRc rate was 75% (42% CR + 33% CRi; 95% CI, 53.3%-90.2%), with a 79% blast clearance rate. Patients 75 years of age or older (n = 29) had a CRc rate of 62% (34% CR + 28% CRi; 95% CI, 42.3%-79.3%), with a 66% blast clearance rate. Patients with adverse-risk cytogenetics by MRC (n = 20) had a CRc rate of 80% (50% CR + 30% CRi; 95% CI, 56.3-94.3), with an 80% blast clearance rate. All 5 patients (100%) who were FLT3/ITD-mutated/nucleophosmin 1 (NPM1)-wild type achieved a remission (CR, n = 4; CRi, n = 1).

Median relapse-free survival was 7.7 months (95% CI, 4.9-15.4), with an 11.3-month (95% CI, 8.8-13.2) median OS (Figure 5A). OS by response status (CR and CRi vs nonresponder) is depicted in Figure 5B, and OS by MRD status is shown in Figure 5C. A similar median OS was observed in older patients (≥ 75 years), in whom median OS was 12.19 months (Figure 5D).
The improved activity achievable with this combination was accompanied by increased on-target toxicity in the form of myelosuppression, as compared with what would be expected with HMAs alone. Grade 3 or higher thrombocytopenia was common, and infection of any grade was reported in 79% of patients, including a sepsis rate of 11%. However, no serious bleeding events (grade 3 or higher) were noted, and the 30- and 60-day mortality of 2% and 8%, respectively, compared favorably with historical data with single-agent HMAs.4,5 The addition of vadastuximab talirine to HMAs clearly increased the intensity of the therapy regimen, yet this combination was delivered safely in the setting of a phase 1 expansion cohort in older patients with AML. Of note, this study was conducted at a limited number of academic medical centers that participated in the preceding monotherapy dose escalation cohorts of the phase 1 trial; therefore, trial sites had extensive experience in the management of profound myelosuppression, seen frequently in treatment of AML and which are also specifically associated with vadastuximab talirine.

In contemporary global randomized phase 3 AML trials of HMA monotherapy for older patients with untreated AML, reported CRc rates were 17.8% for decitabine5 and 27.8% with azacitidine,4

### Table 3. Observed best responses by AML subset

<table>
<thead>
<tr>
<th>All treated (N = 53), %</th>
<th>Secondary AML (n = 24), %</th>
<th>≥75 y old (n = 29), %</th>
<th>FLT3/ITD+ (n = 5), %</th>
<th>MRC adv (n = 20), %</th>
<th>Und. Myelo (n = 23), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>43</td>
<td>42</td>
<td>34</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>CRi</td>
<td>26</td>
<td>33</td>
<td>28</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>mLFS</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CRc rate</td>
<td>70</td>
<td>75</td>
<td>62</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>Blast clearance</td>
<td>74</td>
<td>79</td>
<td>66</td>
<td>100</td>
<td>80</td>
</tr>
</tbody>
</table>

adv, adverse; Int, intermediate; ITD, internal tandem duplication; mLFS, morphologic leukemia-free state; myelo, myelodysplasia; Und, underlying.

Figure 5. Summary of OS. Kaplan-Meier curves are shown depicting OS for all treated patients (A) and by (B) response status (CR vs CRi vs nonresponder), (C) MRD status (MRD-negative CRc vs MRD-positive CRc vs non-responder), and (D) age (<75 years vs ≥75 years). F/U, follow-up; max, maximum; min, minimum; Non-resp = nonresponders.
although comparisons are limited by differences in study design and patient population. As an example, ECOG performance status of up to 2 was frequently permitted in monotherapy studies. Any comparison should be considered with these differences in mind. GO has also been studied in this setting, where CRc rates were 44% and 35% in phase 2 combination studies of GO with azacitidine and decitabine, respectively. In a randomized study of low-dose cytarabine with or without GO in older patients with newly diagnosed AML, the addition of GO improved the CRc rate (30% vs 17%), but did not improve OS. In our study, the addition of vadastuximab talirine to an HMA backbone demonstrated encouraging activity in older patients with AML, achieving a CRc rate of 70% in this phase 1 expansion cohort. However, akin to the GO experience, a similar median OS was observed on this trial compared with historical single-agent HMA data, despite an improved CRc rate.

In addition to full CR, the achievement of CRi with HMA in combination with vadastuximab talirine also appears to be clinically meaningful. A subset of CRi patients attained deep, MRD-negative remission and lengthy durations on study, suggesting that thrombocytopenia in these patients may be a result of on-target myelosuppression, rather than residual leukemia. Patients who achieved MRD-negative CRs had improved survival compared with patients with CRc who remained MRD-positive. Responses were also achieved more rapidly (median time to response: 2 cycles) with this combination than would be expected after single-agent HMA therapy. However, after marrow blast clearance, delays in the start of subsequent cycles were common, as the interval between therapies was lengthened to allow for hematologic recovery in patients who had achieved response. Delays in therapy were left at the discretion of treating physicians at participating academic centers, who had sufficient expertise to provide close clinical care and monitoring, to manage the nuances of hematologic suppression from treatment and the timing of subsequent cycles of treatment with this combination.

Nevertheless, the increased response rate with the addition of vadastuximab talirine to HMAs was also associated with increased toxicity when compared with single-agent HMA therapy, which is indicative of the greater degree of myelosuppression. Forty-nine percent of patients in this expansion cohort experienced febrile neutropenia compared with background rates of 32% with decitabine and 28% with azacitidine. Supportive care and close monitoring were critical in navigating the initial periods of myelosuppression, allowing patients to benefit from the high response rates observed with this combination.

Recent trials have studied various other combinations of novel agents with HMA therapy. The combination of HMAs and venetoclax appears to have a range of efficacy that approximates that reported in the HMA + vadastuximab combination cohort described here. In recently published phase 1 data, venetoclax with HMA therapies produced a CRc rate of 61%. The reported median survival for all 57 patients on that study was 12.3 months. Grade 3/4 thrombocytopenia and neutropenia were also common, seen in 47% and 40% of patients, respectively, and the rate of early death was similarly low. After this encouraging phase 1 experience, larger randomized trials of HMA + venetoclax are ongoing. Other novel HMA combinations are also under study, including those with the NEDD8 inhibitor pevonedistat, the hedgehog pathway inhibitor glasdegib, histone deacetylase inhibitors, isocitrate dehydrogenase 1/2 inhibitors, and various FLT3 inhibitors. Perhaps also relevant to the present cohort, enriched for patients with secondary AML or high-risk disease, are recently published data on CPX-351, a liposomal cytarabine- and anthracycline-based therapy. The phase 3 experience with this agent reported a CRc rate of 47.7% among patients aged 60 to 75 years who had secondary AML, with a median OS of 9.6 months, leading to US Food and Drug Administration approval for the treatment of newly diagnosed therapy-related AML, or AML with myelodysplasia-related changes. Given that patients with secondary AML on CPX-351 were frequently exposed to prior HMA therapies, whereas the HMA + vadastuximab talirine cohort described here excluded patients with prior HMA therapy and those patients deemed candidates for induction chemotherapy, a clear comparison of outcomes between CPX-351 and the HMA combination reported here is challenging. Further, the median age of secondary patients with AML enrolled on the HMA + vadastuximab talirine was 77 years, whereas the CPX-351 trial had an upper age limit of 75 years. Despite the differences in patient populations, the 60-day mortality of 8% observed in the much smaller HMA + vadastuximab talirine cohort reported here appears to be within the same range as the 60-day mortality of 13.7% reported on the CPX-351 phase 3 trial.

On the impressive strength of these phase 1 results, a global, randomized, double-blinded, placebo-controlled phase 3 trial (CASCADE) was launched in 2016 to compare the combination of vadastuximab and HMAs with HMAs alone. The phase 3 trial was terminated early because of increased deaths on the vadastuximab talirine-containing group. Although the data from the CASCADE trial remain under analysis, lack of success on the phase 3 study may demonstrate the difficulties inherent in translating promising phase 1 results to a much larger, global study of an older population of HMA-eligible patients with AML who are more susceptible to toxicity. Future studies with myelosuppressive novel agents in this population, many of whom develop potentially lethal cytopenias, may require more strict protocol-defined guidelines for supportive care and monitoring, including criteria for hospitalization, which would include clinical developments such as fever, severe or progressive bleeding, progressive dyspnea, or hypoxia, among others, as well as mandated use of prophylactic antimicrobials. In addition, the optimal postresponse dose and schedule of vadastuximab talirine has yet to be established; further efforts to identify a dose regimen and cycle interval that maintains remission while minimizing myelosuppression are warranted. With such guidance and precaution, promising combinations for AML, a disease affecting predominantly older and more frail patients, may be more effectively studied so as to enhance our current suboptimal therapeutic options.

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Authorship
Contribution: A.T.F. served as a site principal investigator, performed the research, and participated in data interpretation and writing of the manuscript; H.P.E., J.E.L., E.M.S., F.R., S.F., R.B.W., A.S.A., D.J.D., T.J.K., A.J., D.B., M.Y.L., and A.S.S. served as site principal investigators, performed the research, and participated in data interpretation and editing of the manuscript; and M.M.O., P.A.H., and J.V. designed the trial and participated in data collection, data analysis, and writing of the manuscript.

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25. Burnett AK, Hills RK, Hunter AE, et al; UK National Cancer Research Institute AML Working Group. The addition of gemtuzumab ozogamicin to low-dose Ara-C improves the publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734.

Footnotes

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