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CC-486 (oral azacitidine) in patients with myelodysplastic syndromes with pretreatment thrombocytopenia

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ABSTRACT

Thrombocytopenia is among the strongest predictors of decreased survival for patients with myelodysplastic syndromes (MDS) across all prognostic risk groups. The safety and efficacy of CC-486 (oral azacitidine) was investigated in early-phase studies; we assessed clinical outcomes among subgroups of MDS patients from these studies, defined by presence or lack of pretreatment thrombocytopenia ($\leq 75 \times 10^9$/L platelet count). Patients received CC-486 300 mg once-daily for 14 or 21 days of repeated 28-day cycles. Overall, 81 patients with MDS, median age 72 years, comprised the Low Platelets (n = 45) and High Platelets (n = 36) cohorts. Pretreatment median platelet counts were 34×10^9/L and 198×10^9/L, respectively. Grade 3–4 bleeding events occurred in 2 patients in the Low Platelets and 1 patient in the High Platelets groups; events resolved without sequelae. Treatment-related mortality was reported for 7 patients, 5 of whom had pretreatment platelet values $< 25 \times 10^9$/L. Overall response rates were 38% and 46% in the Low Platelets and High Platelets groups, respectively. Five thrombocytopenic patients attained complete remission and 9 attained platelet hematologic improvement. In both cohorts, platelet counts dropped during the first CC-486 treatment cycle, then increased thereafter. Extended CC-486 dosing was generally well tolerated and induced hematologic responses in these patients regardless of pretreatment thrombocytopenia.

1. Introduction

Myelodysplastic syndromes (MDS) are characterized by ineffective hematopoiesis and peripheral cytopenias. Approximately 40% of all MDS patients, and up to 80% of patients with higher-risk MDS, experience thrombocytopenia, which is typically defined as platelet count $< 100 \times 10^9$/L [1–3]. Thrombocytopenia heightens the risk of transformation to acute myeloid leukemia (AML) and is among the strongest predictors of decreased overall survival (OS) across all International Prognostic Scoring System (IPSS) MDS risk categories [4–7]. A retrospective assessment of the incidence and prognostic significance of thrombocytopenia in 2565 patients with *de novo* MDS showed

Abbreviations: ANC, Absolute neutrophil count; AML, Acute myeloid leukemia; BL, Baseline; BM, Bone marrow; CI, Confidence intervals; CMML, Chronic myelomonocytic leukemia; CR, Complete remission; ECOG, Eastern Cooperative Oncology Group; HI, Hematologic improvement; HI-E, Erythroid HI; HI-N, Neutrophil HI; HI-P, Platelet HI; HMA, Hypomethylating agent; IPSS, International Prognostic Scoring System; IWG, International Working Group; mCR, Marrow CR; MDS, Myelodysplastic syndromes; NCCN, National Comprehensive Cancer Network; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, Overall response rate; OS, Overall survival; PK, Pharmacokinetic; PR, Partial remission; RA, Refractory anemia; RAEB, RA with excess blasts; RARS, RA with ring sideroblasts; RBC, Red blood cell; RCMD, Refractory cytopenia with multilineage dysplasia; TEAE, Treatment-emergent adverse event; TI, Transfusion independence; TPO, Thrombopoietin; WBC, White blood cell; WHO, World Health Organization

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median OS of patients with platelet counts < 30×10^9/L was 7 months, compared with 53 months for patients with platelets ≥30×10^9/L ($P < 0.0001$) [7]. A prognostic MDS risk model developed and validated at the MD Anderson Cancer Center suggests severe thrombocytopenia (counts < 30×10^9/L) has adverse prognostic implications equivalent to those of complex karyotype [8].

There are few therapeutic options for treating thrombocytopenia. The National Comprehensive Cancer Network (NCCN) recommends thrombopoietin (TPO) receptor agonists in cases of severe thrombocytopenia [9]. The TPO receptor agonists, romiplostim and eltrombopag, have been shown to decrease bleeding events in patients with MDS compared with placebo [10–12]; however, clinical studies have had mixed results [10,11,13–15]. Other approaches, such as treatment with the signal-transduction inhibitor, rigosertib, may have efficacy that is limited to certain patients. A post hoc analysis of a phase 3 study of rigosertib vs best supportive care showed a survival benefit for patients who had experienced primary HMA failure rather than secondary HMA failure [16]. Platelet transfusions are associated with a variety of risks, such as febrile or allergic reactions, and frequent platelet transfusions can induce alloimmunization, eventually rendering the patient refractory to transfusions [1]. Injectable azacitidine and decitabine can worsen cytopenias upon initial use, though cytopenias typically resolve as treatment continues [17–19].

Thus, there is a continuing need to discover and develop drugs that can safely and effectively ameliorate thrombocytopenia in MDS. The clinical effects and pharmacokinetics of CC-486, the oral formulation of azacitidine, administered for 7 days per 28-day cycle, and in extended dosing regimens (14- or 21 days per cycle) have been studied in patients with MDS, CMML, and AML in two phase 1/2 clinical studies [20–23]. Currently, CC-486 extended dosing is under investigation in large, randomized phase 3 studies, including a placebo-controlled trial to investigate CC-486 300 mg once-daily in patients with lower-risk MDS with transfusion-dependent anemia and thrombocytopenia (ClinicalTrials.gov NCT01566695). Here we report clinical outcomes with CC-486 monotherapy in patients with MDS from two early-phase clinical studies who had pretreatment thrombocytopenia (≤75×10^9/L platelets), and compare these with outcomes for MDS patients with platelet counts > 75×10^9/L at study entry.

2. Methods

These exploratory, *post hoc* analyses include patients who received CC-486 in an open-label phase 1 study (MDS-004; ClinicalTrials.gov NCT00528983) or an open-label phase 1/2 study (CL005; NCT01519011). All patients provided written informed consent before participating in any procedure-. Appropriate institutional review boards approved the protocols and procedures of the individual studies. Both studies have been completed.

2.1. Patients

Inclusion and exclusion criteria for these studies are described in detail elsewhere [21,23]. Briefly, patients in these analyses were aged ≥18 years, with IPSS lower- or higher-risk MDS and an ECOG performance status score of ≤2. For these analyses, thrombocytopenia was defined as platelet counts ≤75×10^9/L (ie, NCI-CTCAE grade ≥2), creating two subgroups: a "Low Platelets" cohort, comprising patients with baseline platelet counts ≤75×10^9/L, and a "High Platelets" cohort comprising patients with baseline platelet counts > 75×10^9/L.

2.2. Study designs

The two studies evaluated various doses and schedules of CC-486 in patients with MDS, AML, or CMML. The current analysis includes only patients with MDS who received extended dosing with CC-486 300 mg QD for 14 or 21 days per 28-day treatment cycle (these regimens are currently under evaluation in large, phase 3 clinical trials in patients with MDS [NCT01566695] or AML [NCT01757535]).

In the phase 1/2 CL005 trial, CC-486 300 mg QD was administered for 14 days or 21 days per 28-day treatment cycle [21]. In the phase 1 MDS-004 study, patients received 2–3 single CC-486 doses in a pharmacokinetic (PK) evaluation phase, followed by a prospective extension phase in which all patients received CC-486 300 mg QD for 21 days per 28-day cycle [23].

2.3. Endpoints

Treatment-emergent adverse events (TEAEs) were graded by NCI-CTCAE version 3.0 or 3.1. Hematologic responses were defined per International Working Group (IWG) 2006 response criteria for MDS [24]. Composite overall response rate (ORR) included complete remission (CR), partial remission (PR), hematologic improvement (HI), and red blood cell (RBC) or platelet transfusion independence (TI) in patients who were transfusion-dependent at baseline. Marrow CR (mCR) was also assessed as a measure of clinical activity but was not included in ORR. Additionally, subanalyses were conducted to measure HI rates in patient subgroups–regardless of baseline platelet count–defined by baseline IPSS risk [25], World Health Organization (WHO) classification of MDS [26], and bone marrow cellularity. As these were early-phase clinical studies, survival data were not collected.

Because injectable hypomethylating agents, including azacitidine, are associated with exacerbation of cytopenias during early treatment [17], platelet counts during initial CC-486 treatment cycles (excluding measures taken within 7 days after a platelet transfusion) and changes from mean baseline platelet counts during the first 5 CC-486 cycles are reported for both the Low Platelets and High Platelets cohorts, and for responders vs non-responders within the Low Platelets group.

2.4. Statistical analyses

Data are reported descriptively, with no formal statistical comparisons between patient cohorts defined by platelet counts at baseline, or for comparisons in subanalyses based on baseline IPSS risk, WHO MDS classification, or bone marrow cellularity. For ORR, 95% confidence intervals (CI) were determined using a chi-square model.

3. Results

3.1. Patient disposition and baseline characteristics

A total of 81 patients with MDS from the two CC-486 studies had MDS and received CC-486 300 mg QD for 14 or 21 days per 28-day cycle. The Low Platelets (≤75×10^9/L) group comprised 45 patients (16 patients received 14-day dosing with CC-486 and 29 patients received CC-486 for 21 days) and the High Platelets group comprised 36 patients (14-day dosing, n = 13; 21-day dosing, n = 23). Reasons for discontinuation among all patients were: treatment failure (n = 34; 42%), adverse events (n = 22; 27%), withdrawal of consent (n = 5; 6%), proceeding to the optional extension phase (n = 4; 5%), death (n = 4; 5%), or other reasons (n = 7; 9%). Five patients discontinued CC-486 to proceed to stem cell or bone marrow transplant. The median number of CC-486 treatment cycles was 6 (range 1–26) in the Low Platelets cohort and 7.5 (1–33) in the High Platelets cohort.

Median age of all patients was 72 years, and most patients had ECOG performance status scores of 0–1 (Table 1). At entry, patients in the Low Platelets cohort were more likely to have IPSS-defined higher-risk MDS. Low Platelets patients were also somewhat more likely to have a diagnosis of refractory cytopenia with multilineage dysplasia (RCMD). More patients in the High Platelets group had received prior treatment for MDS (72%) than in the Low Platelets group (38%). Prior treatments for MDS received by > 2 patients in the Low Platelets and High Platelets cohorts were erythropoiesis-stimulating agents (n = 11