Oral hypomethylating agents: beyond convenience in MDS

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Oral hypomethylating agents (HMAs) represent a substantial potential boon for patients with myelodysplastic syndrome (MDS) who have previously required between 5 and 7 visits per month to an infusion clinic to receive therapy. For patients who respond to treatment, ongoing monthly maintenance visits represent a considerable burden to quality of life, and for those who are early in therapy, these sequential visits may tax transportation and financial resources that would be optimally distributed over the treatment cycle to facilitate transfusion support. The availability of oral HMAs may support the optimal application of these agents by contributing to adherence and lessening the burden of therapy, potentially encouraging patients to stay on longer-term treatment. Distinct pharmacokinetic profiles for the recently approved oral HMAs (oral azacitidine and decitabine-cedazuridine) result in differential toxicity profiles and have prompted their clinical trial development in lower- and higher-risk MDS, respectively.

LEARNING OBJECTIVES

- Describe the challenges of effective therapy with HMAs for patients with MDS and the barriers to this therapy
- Understand the PK profiles for HMAs given parenterally and contrast these with the PK profiles following oral administration of unmodified oral azacitidine and decitabine/cedazuridine
- Recognize how the PK for oral HMAs may differ from an established parenteral regimen and anticipate the challenges associated with transitioning from one regimen to another

CLINICAL CASE 1

A 78-year-old woman presented to our clinic after routine blood work demonstrated thrombocytopenia and neutropenia. The patient was otherwise in reasonable health for her age with comorbid medically managed hypertension. She was widowed but lived independently, with minimal support from her local adult children. A complete blood count (CBC) at the initial evaluation demonstrated a white blood cell (WBC) count of 1.4×10^9/µL, with an absolute neutrophil count of 0.5×10^9/µL, hemoglobin (Hg) of 11g/µL, and platelet count of 25 k/µL. She was demonstrated to be nutrient replete for B_{12}, folate, iron, and copper. A bone marrow (BM) aspiration and biopsy were performed, showing refractory anemia with excess blast-2 (15% blasts); cytogenetics were normal. Next-generation sequencing (NGS) revealed mutations in *IDH2* and *SRSF2*. A diagnosis of higher-risk myelodysplastic syndrome (MDS) was rendered (International Prognostic Scoring System [IPSS]-Revised [R], 5.5 points [high risk]; IPSS 2.0 points [intermediate-2]), and the patient started therapy with parenteral azacitidine 75mg/m^2 given subcutaneously (SQ) 7 days of a 28-day schedule. The initial treatment was characterized by the development of red blood cell (RBC) and platelet transfusion dependence in cycles 1 and 2. She presented prior to cycle 3 of therapy, and the CBC showed a WBC count of 1.0×10^9/µL with absolute neutrophil count 0.2×10^9/µL, an Hg of 8g/µL, and platelets, 105 k/µL. She came to the clinic accompanied by her children. She stated that she was no longer willing to continue therapy. She reported intolerable loss of quality of life and independence due to the daily infusion clinic visits in the first week of each cycle and the burden of transfusion dependence. She was adamant that she would take no further chemotherapy despite an early response to treatment that suggested she was likely to derive a survival benefit from continued treatment (early hematologic improvement [HI] of the platelet lineage). She requested enrollment in home hospice care and passed away 1 month after therapy discontinuation.Today, the availability of oral agents might have convinced this patient to continue treatment, optimizing her survival and improving her

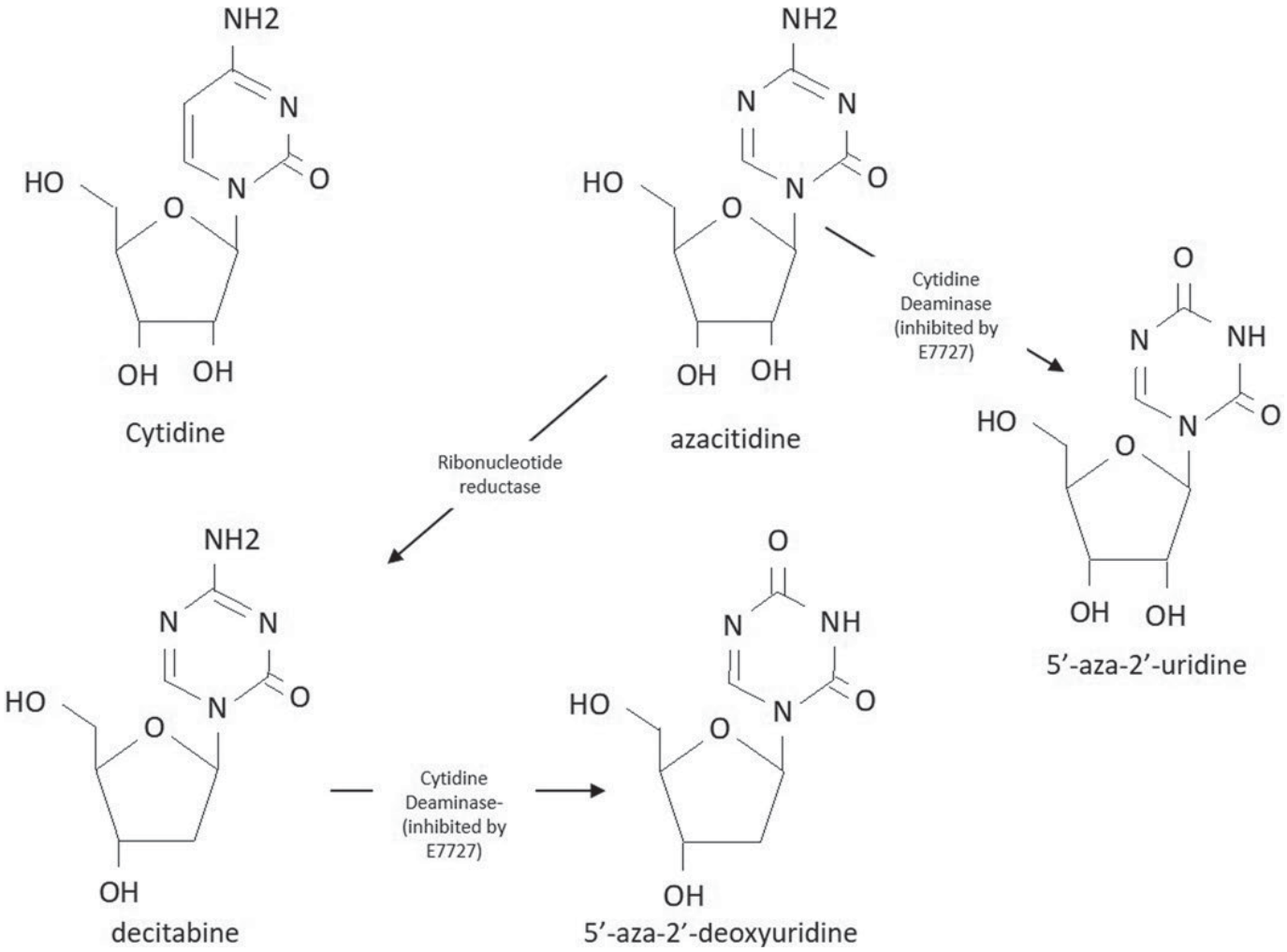

Figure 1. Chemical structure of cytidine, azacitidine analogues, and the breakdown products of CDA.

quality of life. As it stood, this patient accrued all the toxicity from the use of this agent, including initial loss of quality of life, without realizing the longer-term potential benefits of transfusion independence (TI) and survival, which she might have been expected to achieve given her early evidence of response.

Introduction

Hypomethylating agents (HMAs) have been the mainstay of treatment for patients with higher-risk MDS since the initial regulatory approval of monthly treatments with parenteral azacitidine and decitabine in the early 2000s.[1] The shared active metabolite of both agents (~15% of the administered azacitidine dose, converted by the action of ribonucleotide reductase) is decitabine triphosphate, an analogue of the nucleoside cytidine (Figure 1). Although 85% of parenterally administered azacitidine is incorporated into RNA, interrupting protein synthesis and inducing apoptosis, the clinical impact of this incorporation on its activity remains an area of active investigation.[1] When decitabine triphosphate is incorporated into DNA whose parent strand bears a methyl group in the context of a cytosine-phospho-guanine sequence, DNA methyltransferase enzymes (particularly DNMT-1) bind it irreversibly, creating an adduct that results in both DNA damage and the depletion of DNMT enzymes.[2] With repeated cycles of DNA replication, loss of the methylation enzymes results in the passive demethylation of DNA at multiple loci. At low doses that do not cause overwhelming cytotoxicity, these drugs induce transient gene-specific and global hypomethylation that are hypothesized to mediate their response. Historically, activity has been postulated to result from the reexpression of epigenetically silenced tumor suppressor genes, but more recently, reexpression of endogenous retroviral elements with enhanced immune recognition of MDS progenitors has been hypothesized as another putative mechanism.[3] Despite ongoing controversy over the definitive explanation for therapeutic efficacy, optimal patient outcomes from HMA therapy seem to require long-term treatment on a regular and uninterrupted schedule.[4–7]

Dose, schedule, and treatment continuation are critical to optimal HMA response

When given on a monthly basis for repeated cycles, these agents improve cytopenias, lower BM blasts, improve quality of life, decrease transformation to acute myeloid leukemia (AML), and improve survival for select patients.[8–10] Despite years of study, no

effective pretreatment predictors of response are clinically applicable.[11] About half of HMA-treated patients will respond, most with improvements in cytopenias (HI of the affected lineage) and a minority (perhaps 15%) with complete response (CR), but responses can take several months to develop (National Comprehensive Cancer Center guidelines recommend a minimum of 6 cycles of treatment before response assessment) and are generally of limited durability.[12,13] Critically, hematological improvement (HI) in any lineage is associated with survival benefit for patients who continue therapy; with sustained treatment some individuals will have improved blood counts across more than one lineage, even converting to CR.[7,13,14] Unfortunately, when patients discontinue therapy, rapid progression and relapse with poor survival are likely.[15–21] Good responses and improved survival are often accompanied by recovery of the platelet count in the first 1 to 3 cycles of treatment, an early biomarker for those who are likely benefiting from treatment.[22,23]

As for the patient in our first case, early cycles of HMA therapy are often characterized by the worsening of cytopenias and the development of transfusion dependence. This has the potential to create a substantial burden for patients and families, especially since each monthly cycle has historically required 5 to 7 consecutive daily doses of intravenous (IV; decitabine, azacitidine) or SQ (azacitidine) treatment at a designated infusion center. Given the early worsening of cytopenias, optimal supportive care requires weekly or even twice-weekly visits during the subsequent 3 weeks to assess transfusion needs as well as the prophylactic use of antimicrobials.[24] The development of RBC and platelet transfusion dependence and neutropenia early in the course of treatment can trigger clinicians to inappropriately reduce doses, delay, or even discontinue therapy; decisions known to compromise efficacy.[25,26] Such decisions may explain the difference between the survival benefit documented in controlled populations of patients treated with HMAs in the context of clinical trials compared to outcomes in unselected populations of patients, where improved survival rates have been less consistent.[10,21,27,28]

A set of recent retrospective analyses using the surveillance, epidemiology, and end results Medicare-linked database in a large cohort of 644 patients with higher-risk MDS evaluated between 2011 and 2015 sought to investigate the way in which patients treated in a real-world setting routinely receive therapy. This study demonstrated that almost 30% of patients discontinued HMAs before completing 4 cycles—a majority after completing only 1 cycle of treatment.[29] A more detailed analysis of this same cohort reveals that an additional 20% of patients had early dose delays of >90 days between cycles, which likely obviates response.[30] Overall, among the approximately 50% of patients with higher-risk MDS, those who did not receive their HMA on schedule for at least 4 cycles had substantially higher rates of health care utilization characterized by increased emergency room visits, higher rates of hospitalization, and more admissions to skilled nursing facilities and hospice. Suboptimally treated patients in this cohort were more likely to be older and unpartnered.

Real-world studies further demonstrate the relatively limited initiation of HMA treatment for high-risk patients, with only 12% to 30% of presumably eligible patients receiving therapy at all, depending upon the report.[20,27,30] These data highlight the fact that despite the availability of HMAs as primary therapy for MDS for more than 15 years, many patients do not receive any therapy at all, and among those who do, early discontinuation or inadequate dose intensity during early cycles probably compromises response.[30] Such treatment decisions are likely to have an adverse impact on quality of life and compromise survival for those MDS patients, who will accrue all the toxicity from HMA therapy and none of the benefits (HI, CR, or survival) of sustained therapy.[24] The importance of adequate support and therapy persistence for patients with higher-risk MDS cannot, therefore, be overstated.

Oral agents, which might limit the need for treatment-related infusion clinic visits and allow patients a schedule based solely on transfusion needs, have the potential to decrease rates of early discontinuation due to treatment burden and thereby result in improved quality of life, efficacy, and survival for patients with MDS. Furthermore, although most responses to HMAs have been shown to occur within 4 to 6 cycles of treatment, continuation of therapy beyond the first HI results in further improvement in response category for about half of those on treatment.[7,18] Indeed, the best documented response seems to manifest at least 2 to 3 cycles after the first documented HI response, with optimal responses in 1 study manifesting as late as cycle 12 for a majority of patients.[13,18]

Given the ongoing burden of treatment, continued therapy on schedule must be emphasized to patients and should not be underrecognized. Early on, transfusion dependence may increase patient willingness to come to the office for treatment, but in the long term, these visits can become onerous. Ongoing studies are testing whether patients on an established parenteral HMA regimen can be switched to a lower-intensity oral regimen to maximize adherence without compromising efficacy (eg, NCT04806906). Such changes to our therapeutic approach may also improve the real-world outcomes associated with HMA treatment when compared with those seen in clinical trials. If premature discontinuation in responding patients is driven by doctors and patients unwilling to continue therapy, at least in part due to the burden of infusion clinic appointments, I believe oral therapies may help us maximize HMA benefit for patients.

CLINICAL CASE 2

A 69-year-old man with a medical history notable for obesity, diabetes, and bilateral knee osteoarthritis was referred to our practice after a preoperative CBC performed for a planned knee replacement surgery demonstrated thrombocytopenia. The CBC showed a normal WBC count, platelets of 40 000/μL, and anemia with an Hb of 10g; the mean corpuscular volume was 106 fL. The remainder of the CBC and a comprehensive profile were normal, and nutritional workup demonstrated a sufficiency of vitamin B_{12}, folate, and iron; ferritin was 600 (minimally elevated), and the serum erythropoietin level was 580 IU (elevated). The peripheral blood smear was notable for pelgeroid neutrophils, thrombocytopenia, and RBC anisocytosis. A BM aspirate and biopsy were hypercellular and erythroid predominant with 6% blasts and trilineage dyspoeisis. Cytogenetics were 47 XY, +8 in 21 metaphases. NGS was notable for mutations in *TET2* and *ASXL1*. A diagnosis of intermediate-risk MDS (IPSS score, intermediate-1; IPSS-R, 5 points [high risk]) was rendered. After discussion of prognosis and options, he elected to enroll in a phase 1b pharmacokinetic (PK) study of oral decitabine-cedazuridine fixed-dose tablet 35mg/100mg. Initial cycles were characterized by grade

Table 1. PK characteristics of the HMAs

Agent	Bioavailability of single oral dose (% of parenteral)	$T_{1/2}$	T_{max} (range)	C_{max} in ng/mL (% coefficient of variation)
Azacitidine IV[34,40]	100%	4h	0.5h	Similar to SQ
Azacitidine SQ[34,40]	89%	4h	0.5h (0.2–1.1)	750 (54%)
CC-486[40,52]	11%	0.5h	1h (0.47–2)	145 (64%)
Decitabine IV[35]	100%	0.5h	1h	147 (49%)
Decitabine PO[41]	3.9%-14.1%	0.36–0.93h	0.5h	—
C-DEC[43]	60% (55–65) D1; 106% (98–114) D5	1.5h	1h (0.3–3.0)	145 (55%)

4 thrombocytopenia and neutropenia and platelet transfusion dependence. After cycle 5 the patient had recovery of the platelet count. A BM biopsy after cycle 4 demonstrated a blast percentage of 4% with ongoing dysplasia. Referral for transplant was made, and a fully matched sibling donor was identified. The patient currently remains on protocol cycle 12 of oral decitabine-cedazuridine, given 4 days of a 28-day cycle (the dose was reduced after cycle 8 for neutropenia lasting more than 2 weeks and BM showing ongoing therapeutic response). He has declined to proceed with transplant due to concerns about transplant-related mortality. He enjoys an excellent quality of life and remains transfusion independent (TI) and nonneutropenic with a platelet count above 100 k/μL. These counts allow him to use nonsteroidal agents for management of his knee pain without bleeding risk.

PKs of parenteral vs oral HMAs

Parenteral daily HMA treatment with azacitidine and decitabine results in blood drug levels that peak between 15 and 30 minutes after administration and an elimination half-life between 1 to 2 hours for azacitidine and 35 to 40 minutes for decitabine (Table 1).[31–35] The short half-life of parenterally administered HMAs is mediated largely by the ubiquitous expression of the enzyme cytidine deaminase (CDA), which is highly expressed in a variety of human tissues, including the liver, the BM, and the gastrointestinal (GI) tract. CDA rapidly degrades these agents into the inactive metabolites of uridine (Figure 1).[32,36]

The early development of oral HMAs was characterized by the recognition that when given alone oral administration results in markedly lower peak plasma concentrations with a wide range of bioavailability when compared with IV or SQ dosing strategies.[33,37–41] Table 1 provides a comparison of half-life, single-dose bioavailability (based upon area under the concentration time curve), time to maximal blood drug level (Tmax), and maximal blood concentration achieved after the administered dose (Cmax) for each drug depending upon the route of administration. Differences in bioavailability are mediated by wide inter- and intraindividual ranges of CDA expression, with higher levels in men, in those with specific single-nucleotide polymorphisms, and in the context of inflammatory drivers.[32,36,42]

Oral decitabine/cedazuridine

Based upon the demonstration of pharmacological equivalence to IV decitabine, in July 2020 the US regulatory authorities approved the first oral HMA, decitaine-cedazuridine (C-DEC: 35/100mg), for patients with higher-risk MDS (intermediate/high risk by IPSS).[43] In contrast with another recently approved agent, unmodified oral azacitidine (CC-486), which will be discussed subsequently, C-DEC has been shown in a randomized phase 3 study to reliably recapitulate the blood drug levels over time (cumulative area under the concentration-time curve; AUC_{∞}; Figure 2) resulting from daily treatment for 5 days with IV decitabine, and the 2 can therefore be treated interchangeably for the purposes of clinical management.[44,45]

As expected, based upon the ubiquitous expression of CDA in the liver and GI tract, there is substantial first-pass metabolism of oral decitabine. Single-agent oral decitabine was shown in a phase 1 study to result in low bioavailability with substantial variation across individuals when compared with IV decitabine.[41] To overcome the variable PKs resulting from differential CDA levels within and across individuals, a novel inhibitor of CDA (CDAi) given the designation E7727 (subsequently cedazuridine) was developed and extensively tested in animals.[46] This agent demonstrated excellent bioavailability and a wide safety margin in nonhuman primates.[46,47] In a series of early-phase studies, the combination of cedazuridine with oral decitabine (developed initially as ASTX 727 and subsequently designated decitabine-cedazuridine) was tested to develop a combination pill designed to recapitulate the PK and pharmacodynamic (PD) administration of IV decitabine dosed at 20mg/m^2 for 5 days.[47] Serial blood collection was performed, and changes in global methylation using the repetitive DNA sequence long interspersed nuclear element 1 (a surrogate for global DNA methylation) was used as a tool for comparing pharmacodynamic (PD) efficacy.[48] Given the substantial intra- and interindividual variability in CDA levels, the development program for this agent used each patient as their own control and compared the PK/PD for IV decitabine against the PK/PD for the oral combination.[47–49] Early studies used PK/PD readouts to titrate the oral doses of E7727 and decitabine in order to create a near identity with IV decitabine administration (Figure 2a). Ultimately, the 2 were combined into a fixed-dose combination tablet containing 35mg of decitabine and 100mg of cedazuridine.[43–45]

The phase 3 study of C-DEC, upon which approval was based, randomized and treated 133 patients in a crossover design to receive either sequence A: C-DEC orally for 5 out of 28 days in cycle 1 followed by IV decitabine 20mg/m^2×5 out of 28 days in cycle 2 and subsequently C-DEC for cycles 3 onward or sequence B: IV decitabine 20mg/m^2×5 out of 28 days in cycle 1 followed by C-DEC orally daily for 5/28 days in cycle 2 and subsequently

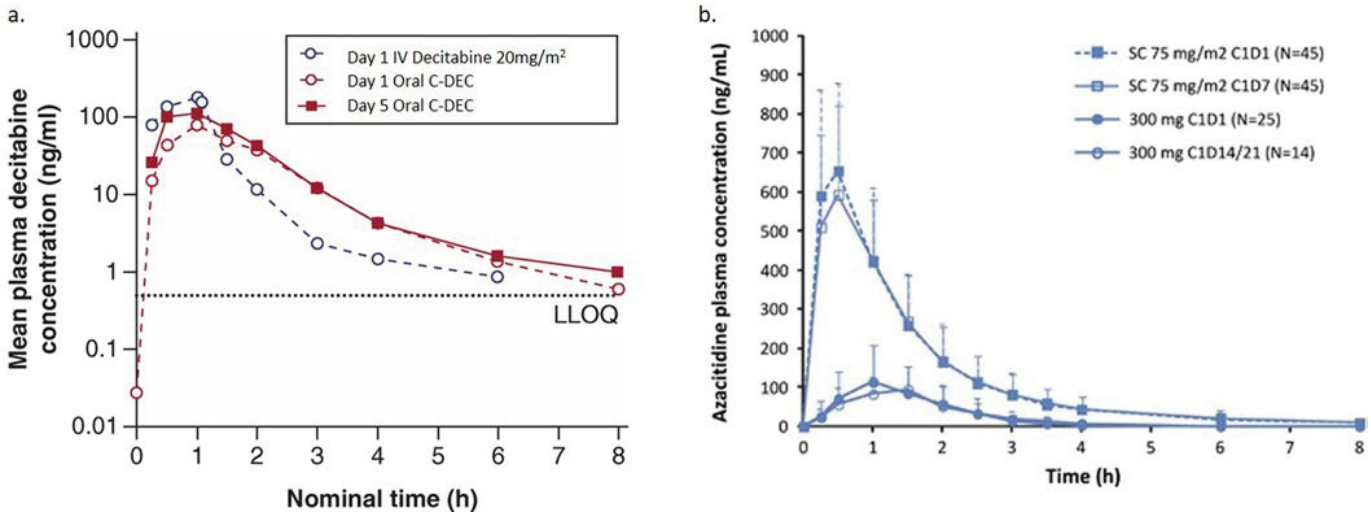

Figure 2. Concentration time curves for (a) IV decitabine vs oral C-DEC and (b) SQ azacitidine vs CC-486.[40,46] Figure 2a was reproduced from *Future Oncol*. 2021;17(16):2077–2087 and was modified only by renumbering for the purpose of this article. Figure 2b was reproduced from *Leukemia* 2016;30(4):889–896 and was also modified only by renumbering. Both works are licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. http://creativecommons.org/licenses/by-nc-nd/4.0/

C-DEC for cycles 3 onward; cycles were to be repeated every 28 days (Figure 3). The primary end point for this phase 3 study was PK for cumulative AUC equivalence between IV and oral dosing of decitabine. Eligible patients had MDS by French-American-British classification, including chronic myelomonocytic leukemia, or MDS deemed intermediate 1, 2, or high risk by the IPSS. The clinical response to therapy was assessed according to International Working Group 2006 criteria by an independent review committee. Enrolled patients were of median age 71 years (range, 44–88), 65% were male, 12% had chronic myelomonocytic leukemia, the remainder had MDS, and 42% had >5% marrow blasts. Transfusion dependence for either RBCs or platelets was present in 43%. After a median follow-up of 12.6 months, complete remission was reported in 28 (21%) and HI in 30 (23%) patients for an overall response rate of 43%. An additional 23 patients demonstrated marrow CR without HI, although blast clearance without blood

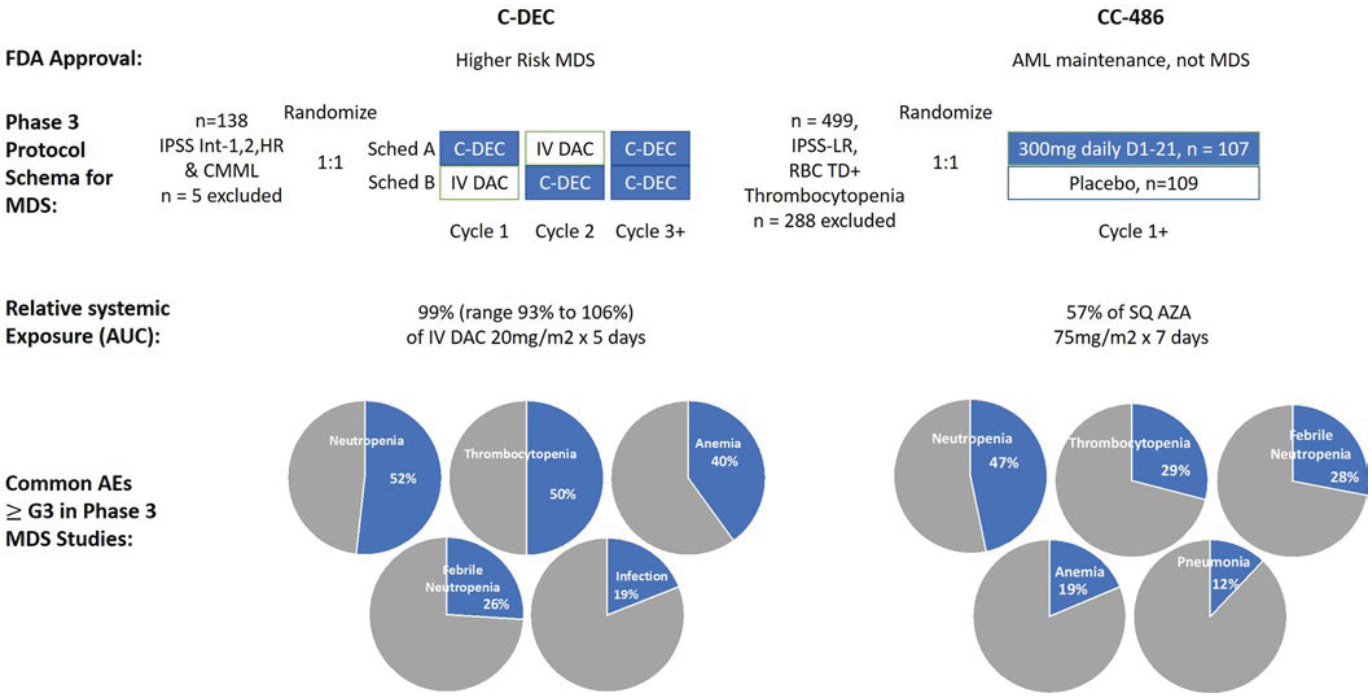

Figure 3. Summary comparison of the 2 completed phase 3 studies of C-DEC and CC-486 in MDS. Data abstracted from Garcia-Manero et al[40,49,55] and Savona et al.[45] AZA, azacitidine; DAC, decitabine.

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