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CASE REPORT

# Rapid loss of response after withdrawal of treatment with azacitidine: a case series in patients with higher-risk myelodysplastic syndromes or chronic myelomonocytic leukemia

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## Abstract

In patients with myelodysplastic syndromes (MDS), the likelihood of having a sustained response to azacitidine is increased by maximizing treatment duration. This is important as prognosis postrelapse is poor. There is also the concern that early termination of treatment may result in rapid disease progression. We reviewed outcomes in 13 patients who discontinued azacitidine (decitabine in one patient) while still responding to the treatment. Most patients rapidly relapsed; median time to progression was 5.4 months. Reasons for treatment discontinuation included comorbidities, infections, and patient choice. These findings illustrate the risk of prematurely terminating azacitidine therapy in MDS.

**Key words** myelodysplastic syndromes; chronic myelomonocytic leukemia; hypomethylating agents; azacitidine

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Myelodysplastic syndromes (MDS) constitute a heterogeneous group of clonal hematopoietic disorders that primarily affect the elderly and are characterized by bone marrow failure, dysplasia, and increased risk of developing acute myeloid leukemia (AML). Patients with untreated higher-risk disease (International Prognostic Scoring System [IPSS] intermediate (Int)-2-/high risk) have a poor prognosis with a median survival of approximately 1 yr or less.

The hypomethylating agent therapy (HMT), azacitidine (Vidaza®, Celgene Corporation, Summit, NJ), improves survival vs. conventional care regimens in higher-risk MDS. Azacitidine treatment is also associated with delayed disease progression, reduced transfusion requirements, and enhanced quality of life (1). Azacitidine is usually well tolerated in very elderly patients (2) and patients with significant comorbidities (3). Based on these findings, azacitidine has become established as the standard of care for the treatment of patients with higher-risk MDS who are ineligible for stem cell transplantation (SCT). Azacitidine is also indicated for patients with World Health Organization (WHO)-defined AML (20–30% blasts) and chronic myelomonocytic leukemia (CMML) (4).

Several treatment cycles may be required before patients respond to azacitidine. In the phase III AZA-001 trial, 87% of responders achieved their first response within six cycles. Of these patients, 48% achieved improved responses with continued dosing after the first response (5). Moreover, terminating treatment in responding patients may quickly lead to the return of aberrant promoter methylation and gene silencing, resulting in accelerated relapse (5). It is important,

therefore, that patients are treated until disease progression to maximize the chance of achieving a prolonged response.

To assess the consequences of early azacitidine discontinuation, we describe clinical outcomes in a series of 13 patients treated with HMTs (one patient was treated with decitabine) who discontinued treatment while still responding.

## Patients and methods

Clinical data were retrospectively collected from 13 patients diagnosed with high-risk MDS or CMML and treated with HMTs at eight Italian hematology centers between April 2003 and July 2011. Inclusion criteria were diagnosis of high-risk MDS or CMML and HMT discontinuation while still responding (including complete or partial remission [CR or PR], or hematologic improvement [HI]). Treatment response was defined according to modified IWG criteria (6). The study was approved by the institutional review boards.

Of the 13 patients, six were male and seven were female. Median age at diagnosis was 69 yr (range, 42–84 yr), and median baseline white blood cell count, hemoglobin concentration, and platelet count were $2.5 \times 10^9$/L (range, 1.5–25.0), 10.6 g/dL (range, 7.4–13.3), and $61 \times 10^9$/L (range, 27–200), respectively.

Patients were classified using the WHO classification system: 11 of 13 patients were diagnosed with refractory anemia with excess blasts-II, one patient was diagnosed with refractory cytopenia with multilineage dysplasia, and one patient was diagnosed with CMML. Seven patients had a normal karyotype, five patients had abnormal karyotypes (two had monosomy 7; one had complex karyotype), and one patient was not evaluated. Nine patients were classified as IPSS Int-2-risk and four as high risk. The MDS-specific comorbidity index (MDS-CI) (6) before initiation of therapy is reported in Table 1.

Patients received a median 10 treatment cycles (range, 5–31). Of 12 patients treated with azacitidine, nine received the approved dose of 75 mg/m$^2$/d for 7 d of every 28-d cycle, two received 100 mg/m$^2$/d for 7 d, and one received 50 mg/m$^2$/d for 10 d. The patient treated with decitabine received 45 mg/m$^2$/d for three consecutive days administered every 6-wk cycle (8).

## Results

Seven patients achieved CR, one patient achieved PR, and five patients achieved HI. Best response was achieved after a median four cycles (range, 3–9). Overall, 46% of patients (6/13) experienced WHO grade 3–4 adverse events (AEs) during treatment (Table 1). Four patients experienced AEs considered related to azacitidine (one skin erythema, one necrotizing fasciitis at the azacitidine injection site, one grade 3 bowel occlusion during cycle 16, and one anemia during cycle 1).

**Table 1** MDS-CI, AEs, and reasons for cessation of HMT

| Patient | MDS-CI[1] | WHO grade 3–4 AEs | Reason for therapy cessation |
|---|---|---|---|
| 1 | 1 (severe pulmonary disease) | – | Acute exacerbation of COPD |
| 2 | 1 (solid tumor) | – | Decitabine stopped according to EORTC protocol (7) |
| 3 | 0 | – | Patient choice |
| 4 | 1 (cardiac disease) | – | Acute myocardial infarction |
| 5 | 3 (cardiac, renal disease) | Cutaneous | Cutaneous erythema |
| 6 | 0 | – | Patient choice |
| 7 | 0 | Cutaneous | Necrotizing fasciitis at HMT injection site |
| 8 | 3 (severe pulmonary, cardiac disease) | Cardiac | Ventricular fibrillo-flutter, pneumonia |
| 9 | 2 (cardiac disease) | Abdominal abscess | Diverticulitis, pneumonia |
| 10 | 2 (cardiac disease) | Bowel occlusion | Bowel occlusion |
| 11 | 2 (solid tumor, severe pulmonary disease) | – | Poor performance status |
| 12 | 2 (cardiac disease) | Anemia | Heart complications |
| 13 | 2 (cardiac disease) | – | Patient choice |

AEs, adverse events; COPD, chronic obstructive pulmonary disease; EORTC, European Organisation for Research and Treatment of Cancer; HMT, hypomethylating agent therapy; MDS-CI, MDS-specific comorbidity index; WHO, World Health Organization.
[1]According to Della Porta *et al.*, Haematologica 2011 (7).

All patients terminated treatment while still responding to HMT. Reasons for discontinuation are listed in Table 1. Recurring reasons included underlying comorbid conditions such as cardiac complications and chronic obstructive pulmonary disease (COPD), unresolved AEs such as infections, complications of cutaneous reactions and bowel occlusion, and patient choice.

Stability of response had been confirmed in 10 of 13 patients who underwent a bone marrow aspirate shortly before treatment stop (median of 1.6 months, range 8.4 months before and 1.9 months after stop). Following cessation of HMT, 77% of patients (10/13) progressed after a median 5.4 months (range, 1.2–27.1), a median 13.2 months (range, 2.6–38.3 months) after achievement of best response. In the five patients achieving HI, progression was characterized by increase in bone marrow blasts in one patient, two patient lost transfusion independency, and two patients had no signs of progression and stopped due to exacerbation of comorbidities (UPN 10 and 11). There were no correlations between treatment response and presence of comorbidities at the time of therapy initiation. However, comorbidities and exacerbation of AEs during treatment led to HMT withdrawal in eight patients (Table 1).

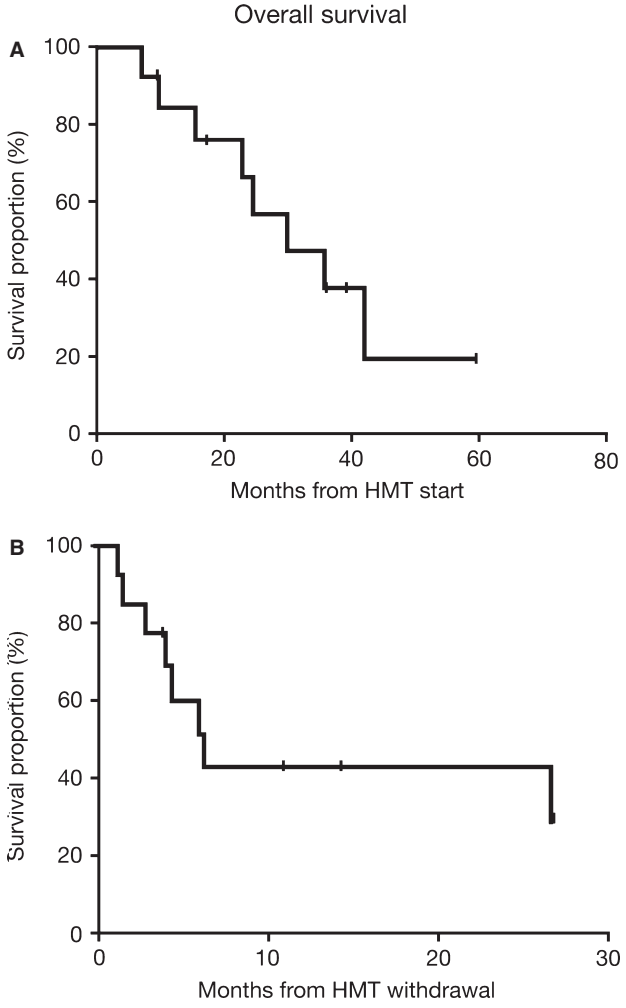


**Figure 1** Kaplan–Meier curves of survival from (A) after start of HMT and (B) after cessation of HMT. HMT, hypomethylating agent therapy.

At a median follow-up of 24.5 months after the start of HMT, eight of the 13 patients had died. Among those still alive at follow-up, all except one patient had progressive disease. Median overall survival (OS) was 29.8 months (range, 7.2–59.6 months) from HMT start and 6.6 months (range, 1.4–27.2 months) from HMT withdrawal (Fig. 1).

## Discussion

This retrospective study illustrates the risk of discontinuing HMT in patients with MDS or CMML while still responding to the treatment. The majority of our patients experienced rapid disease progression and died shortly after treatment cessation. Of course we cannot exclude that some patients would have progressed also with continuing treatment, but bone marrow aspirates performed shortly (about 2 months) before or after HMT discontinuation had shown stability of counts in 10 of 13 patients. Rapid disease progression after treatment interruption appears to be in line with the demethylating effect of HMT, which, in contrast to pure cytotoxicity, is reversible, and continuous administration is necessary to maintain efficacy (9).

Prognosis of patients following discontinuation or failure of HMTs is very poor. Disease progression is particularly problematic due to a lack of standardized salvage therapy options. HMT re-treatment is an option, but quality and duration of second responses are inferior when compared with frontline HMT (10). Few patients are eligible for SCT or intensive chemotherapy, and there is a major unmet medical need for novel agents that improve survival in this setting (11). In a recent retrospective study of 435 patients, median OS after azacitidine failure was only 5.6 months and 2-yr survival was 15% (11). Outcomes were particularly poor in elderly patients, and those with high-risk cytogenetics or a high bone marrow blast count. In another study, patients who relapsed following decitabine treatment had a similarly poor outlook (12).

One of the primary reasons for premature discontinuation of azacitidine therapy in this study was development, or exacerbation, of comorbid conditions including cardiac complications and COPD. Population-based studies have shown that patients with comorbidities are less likely to be prescribed HMTs than those without (13). However, recent data have demonstrated that comorbidities should not necessarily preclude initiation, or continuation, of azacitidine therapy. In a retrospective study of 103 patients with MDS treated with azacitidine, response rates were similar regardless of comorbidity score (3). Treatment could be administered to patients with comorbidities without a substantial increase in AEs. Moreover, the survival benefit persisted also when compared to age- and diagnosis-matched historic controls in all patients except those with very high comorbidity burdens (3). On the other hand, Itzykson *et al.* reported that poor performance status (Eastern Cooperative Oncology Group $\geq$ 2) was associated with shorter OS in a series of 282 consecutive Int-2-risk/high-risk MDS patients treated with azacitidine (14). In this study, data had been collected from a compassionate patient-named program, including frail patients who are usually excluded from clinical trials (14).

Four patients in this study discontinued treatment due to AEs including infections such as pneumonia. Infections are a known complication in patients with MDS and may be exacerbated by azacitidine-related myelosuppression that typically occurs during the first few cycles (15). This can lead to initial deterioration of the clinical condition of frail patients, which may prompt clinicians to terminate treatment. In the AZA-001 trial, there were 14 cases of pneumonia in patients treated with azacitidine. However, these cases were effectively managed by concomitant antibiotics and dose reductions/interruptions (15). Given the risks of terminating treatment, it is recommended that physicians closely follow guidelines regarding the on-treatment management of AEs, before considering discontinuation (4).

Finally, three treatment discontinuations in this study were due to patient choice. A recent Internet survey of 358 patients with MDS indicated that patient understanding of disease characteristics, prognosis, and treatment goals was very limited (16). It is possible that some patients choose to terminate treatment without full appreciation of the likely consequences. This may be improved by better physician–patient communication.

In summary, outcomes in patients with higher-risk MDS treated with azacitidine or decitabine are optimized if treatment is continued until disease progression. Physicians need to be aware of the risks of (i) terminating treatment while patients are still responding and (ii) emerging data regarding the effective treatment of frail elderly patients with comorbidities and management of AEs while on treatment.

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## Author contributions

MTV designed the study and wrote the manuscript; MB, ML, AP, PN, CF, AB, PM, and RZ collected patient data and revised the manuscript; LF analyzed patient data; GA contributed cases and revised the manuscript; GL revised the manuscript.

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