Azacytidine Failure Revisited: an Appraisal Based on Real-Life Data from the MDS Registry of the Hellenic Myelodysplastic Syndrome Study Group (HMDS).

Keywords: MDS, Azacytidine, Prognostic models.

To the editor.

5-azacytidine (AZA) is the mainstay of treatment for high-risk MDS,1 but both primary and secondary, i.e., after an initial response, AZA failure confers a grave prognosis.2,3 Allogeneic transplantation and trials definition of AZA failure and the decision to availability of subsequent treatment options, the exact real-life settings day cycles. Granulocyte colony-stimulating factors and drugs in the setting of AZA failure. patients may confuse the results of trials with novel to assume that the diverse prognosis of the above everyday clinical practice. Furthermore, it is plausible to discontinue AZA is of particular importance in severe myelotoxicity or myelosuppression -related displacements of the treating physician. Dose reductions of erythropoiesis-stimulating agents were used at the discretion of the treating physician. Dose reductions of 25%-50% and/or treatment delays were considered for severe myelotoxicity or myelosuppression-related complications. Treatment response was evaluated using the IWG 2006 criteria.6 Survival analysis was performed using a Kaplan-Meier estimate and Cox’s proportional hazards model. Overall survival (OS) was defined as the time from AZA initiation or failure to last follow up or death from any cause. Akeaike Information Criteria with correction for finite sample sizes (AICc) was used to compare model fits.7

Table 1 lists the patients’ characteristics. After a median follow-up of 41.7 months, the median OS from AZA initiation for the whole cohort was 14 (95% CI: 12.6–15.4) months. Though not designed for patients with MDS/MPN and low-risk IPSS the French Prognostic Scoring System (FPSS)8 was the better survival discriminator compared to IPSS and IPSS-R (Figure 1A, AICc 1958,841 vs. 2276,767 vs. 2321,742, respectively). In multivariate analysis, FPSS (p<0.001), the best response to AZA (p<0.001) and, marginally, disease subtype (MDS/MPN vs others, p=0.01) were all independent predictors of OS (supplementary Table 1).

The median time to AZA discontinuation was 7.5 months (95% CI: 6.5–8.5) with 43 (13.2%) patients still receiving AZA at the time of analysis. The median OS from AZA failure (n=252), defined as AZA intolerance, no response after at least 4 cycles along with AZA intolerance, progressive disease or death while on treatment, and loss of response, was 5.6 (95% CI: 4.8–6.3) months, similar to the one reported in other studies.2,3 Progressive disease while on treatment (n=77, 28%) and AZA intolerance (n=88, 31%) were the most common causes of AZA failure, followed by loss of an initial response (n=41, 15%) and no response after 4 cycles (n=25, 9%). Median OS after AZA failure was comparable for all of the above causes (p=0.1, Figure 2), indicating that the diverse pathobiology behind AZA failure does not influence the outcome and rather typical clinical parameters at the time of AZA failure, as those captured by the post-HMA model, determine patient survival. However, the 20% rate of early discontinuation and 7% rate of early...
Table 1. Clinical information of 326 patients.

| Parameters (median, range) | (at AZA initiation, n=326) | (at AZA discontinuation, n=283) |
|---------------------------|-----------------------------|---------------------------------|
| Age                       | 73.6 (34.6-88.8)            | 74.3 (34.7-88.5)                |
| >65                       | 69 (21.1%)                  | 59 (21%)                        |
| <65                       | 257 (78.9%)                 | 224 (79%)                       |
| Sex                       |                             |                                 |
| Male                      | 223 (68.4%)                 | 193 (68%)                       |
| Female                    | 103 (31.6%)                 | 90 (32%)                        |
| WHO classification        |                             |                                 |
| RCMD                      | 19 (5.9%)                   | 16 (5.7%)                       |
| RAEB-I                    | 60 (18.4%)                  | 50 (17.6%)                      |
| RAEB-II                   | 137 (42%)                   | 115 (40.7%)                     |
| CMML/ MDS/MPN             | 47 (14.4%)                  | 43 (15.2%)                      |
| Low blast count AML       | 63 (19.3%)                  | 59 (20.8%)                      |
| Baseline counts           |                             |                                 |
| Hemoglobin (g/dl)         | 9 (4.3-14.7)                | N/A                             |
| ANC (x 10⁹/L)             | 0.91 (0.03-10.5)            | N/A                             |
| Platelets (x 10⁹/L)       | 74 (3-553)                  | 39 (1-520)                      |
| Bone marrow blasts        | 12 (1-29)                   | 18 (1-87)                       |
| IPSS                      |                             |                                 |
| Low/Intermediate-1        | 77 (23.6%)                  |                                  |
| Intermediate-2            | 149 (45.7%)                 |                                  |
| High                      | 82 (25.2%)                  |                                  |
| N/A                       | 18 (5.5%)                   |                                  |
| WPSS                      |                             |                                 |
| Low/Intermediate-1        | 20 (6.1%)                   |                                  |
| High                      | 136 (41.7%)                 |                                  |
| Very high                 | 55 (16.9%)                  |                                  |
| N/A                       | 115 (35.5%)                 |                                  |
| IPSS-R                    |                             |                                 |
| Low                       | 36 (11%)                    |                                  |
| Intermediate              | 53 (16.3%)                  |                                  |
| High                      | 119 (36.5%)                 |                                  |
| Very high                 | 96 (29.4%)                  |                                  |
| N/A                       | 22 (6.7%)                   |                                  |
| FPSS (GFM)                |                             |                                 |
| Low                       | 38 (11.7%)                  |                                  |
| Intermediate              | 199 (61%)                   |                                  |
| High                      | 33 (10.1%)                  |                                  |
| N/A                       | 56 (17.2%)                  |                                  |
| Post HMA model            |                             |                                 |
| Low                       | -                           | 64 (22.7%)                      |
| High                      | -                           | 134 (47.3%)                     |
| N/A                       | -                           | 85 (30%)                        |
| IPSS Cytogenetic risk     |                             |                                 |
| Good                      | 177 (54.3%)                 |                                  |
| Intermediate              | 60 (18.2%)                  |                                  |
| Poor                      | 71 (21.8%)                  |                                  |
| N/A                       | 18 (5.5%)                   |                                  |
Table 1. Distribution of patient characteristics based on IPSS-R cytogenetic risk.

| IPSS-R Cytogenetic risk | n (%) |
|-------------------------|-------|
| Good/Very Good          | 179 (54.9%) |
| Intermediate            | 61 (18.7%) |
| Poor                    | 34 (10.4%) |
| Very poor               | 34 (10.4%) |
| N/A                     | 18 (5.5%) |

| Number of completed cycles | Median (range) |
|----------------------------|----------------|
|                             | 7 (1-59)       |

| Red cell transfusion dependency | Yes     | No     | N/A    |
|---------------------------------|---------|--------|--------|
|                                 | 216 (66.3%) | 93 (28.5%) | 17 (5.2%) |

| Best response | CR+CRi+PR | Hematologic improvement (platelets +/- neutrophils) | Stable disease | Failure | N/A    |
|---------------|----------|------------------------------------------------------|---------------|---------|--------|
|               | 87 (26.7%) | 60 (18.4%)                                           |               | 91 (28.2%) | 17 (5.2%) |

Abbreviations: IPSS = International Prognostic Scoring System, IPSS-R = revised International Prognostic, Scoring System, WPSS = World Health Organization classification-based Prognostic Scoring System, FPSS = French Prognostic Scoring System, RCMD = refractory cytopenia with multilineage dysplasia, RAEB = refractory anemia with excess blasts, CMML=chronic myelomonocytic leukemia, AML=acute myeloid leukemia, MDS/MPN=Myelodysplastic/myeloproliferative neoplasm, N/A=not available/applicable

Figure 1. Overall survival at azacytidine initiation and at the time of azacytidine failure.
(A) Kaplan-Meier analysis by IPSS, IPSS-R and FPSS patient stratification at azacytidine initiation. (B) Overall survival after azacytidine failure, i) according to the post-HMA model, ii) in IPSS low/intermediate-1 risk vs all other patients and iii) in patients who continued or immediately stopped azacytidine after losing the initial response.
Figure 2. Causes of AZA failure and their effect on outcome.
(A) Failure causes in the patient cohort (n=280). Other causes include second neoplasms, local treatment policies and inclusion in clinical trials. (B) Overall survival after AZA failure according to the reason of failure. Early death, patient’s decision and other causes were excluded from the analysis (n=225). PD: progressive disease.

despite being lower-risk patients (n=54), the OS of our cohort, limited to patients with IPSS lower-risk score, was only 4.7 (95% CI: 1.6–7.8) months similar to that of the high-risk patients (n=172, Figure 1B). Though not easily interpretable, this inconsistency may be
attributable to selection biases due to clinical judgment in real-life settings, i.e., administration of AZA mainly in poor prognosis, multi-treated patients. Indeed, at AZA initiation, only 24/75 (32%) of IPSS lower-risk patients were categorized as low risk by IPSS-R and 13/57 (23%) by FPSS. In addition, at the time of HMA failure 31/41 (76%) of the evaluable IPSS lower risk patients fell into the post-HMA high risk category, although, as expected, significantly more IPSS, WPSS and IPSS-R higher risk patients were classified as high risk by the post-HMA model (supplementary Figure S1).

After AZA discontinuation, most patients were treated with supportive care, and only 9 patients proceeded to allo-SCT. Median OS after AZA failure was identical among patients treated with best supportive care, low dose AraC and intensive chemotherapy (p=0.22), whereas 14 patients treated with decitabine showed significantly improved mOS compared to all other treatments (21.1, 95% CI: 12–30.1 months, p=0.003, Supplementary Figure S2).

Regarding the above patients, 5/11 evaluable cases were low and 6/11 high risk by post-HMA, whereas 4 compared to all other treatments (21.1, 95% CI: 12–30.1 months, p=0.003, Supplementary Figure S2). The overall response rate with decitabine treatment. can be made, though selected patients who failed AZA may benefit significantly by the continuation of AZA compared to the ones who stopped treatment. By contrast, prolonged survival was recently reported in patients who stopped AZA or decitabine without disease progression, but the study cohort consisted mainly of IPSS low-risk patients, most of whom discontinued treatment for extra medical causes.

In summary, in our large patient dataset, we confirmed the superior efficacy of FPSS and post-HMA models in predicting OS at AZA start and failure, respectively. However, our data also indicate that in real life settings, AZA failure is rather ill-defined, and physicians’ perceptions of the cause and timing of AZA discontinuation differ widely. Retrospective data are inherently susceptible to selection and analysis bias. Specifically for the setting of AZA failure, the highly diverse reasons of AZA discontinuation in our series emphasize that, since no uniform criteria for stopping AZA have been adopted, any survival comparisons should be given with caution. Failure due to intractable toxicity and disease progression confers very poor outcome, while patients who lose the initial response may benefit from AZA continuation despite poor prognostic features, highlighting, on the one hand, the diversity of the resistance mechanisms to AZA and, on the other, the limitations of the applicability of prognostic models and response criteria in everyday clinical practice.

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Supplemental Data

Supplementary Figure S1. Distribution of patients by the post-HMA model (n=198).
Patient disposition to the post-HMA risk categories according to their initial classification in IPSS, WPSS and IPSS-R models at AZA initiation. As expected significantly more higher-risk patients fell into the post-HMA high-risk category compared to the lower risk ones. However, these differences are not observed with FPSS.

Supplementary Figure S2. Treatment modalities after AZA discontinuation (n=254).
(A) Treatments after AZA discontinuation (n=254). BSC: best supportive care +/- hydroxurea; IC: intensive chemotherapy; LDAC: low dose AraC; DAC: decitabine; Allo-SCT: allogeneic stem cell transplantation; AZA: retreatment with AZA after an interruption of >3 months (n=2). (B) Overall survival after AZA failure according to treatment modality. Allogeneic stem cell transplantation (Allo-SCT) and AZA retreatment were excluded from the analysis due to the very low number of cases.
Supplementary Figure S3. Overall survival at azacytidine initiation according to WHO subtype (n=326). Overall survival (OS) in first line azacytidine treated patients. Overlapping myeloproliferative/Myelodysplastic syndromes and CMML (collectively shown as MDS/MPN) diagnosis conferred significantly lower median OS compared to all other WHO subtypes. RCMD = refractory cytopenia with multilineage dysplasia; RAEB = refractory anemia with excess blasts; CMML = chronic myelomonocytic leukemia; AML = acute myeloid leukemia; MDS/MPN = Myelodysplastic/myeloproliferative neoplasm.

Supplementary Table 1. Multivariate analysis of prognostic factors for overall survival after AZA initiation in the whole patient cohort (n=326; 253 with full data).

|                      | Univariate analysis | Multivariate analysis |
|----------------------|---------------------|----------------------|
|                      | Median OS | p-value | HR (95% CI) | p-value |
| Age                  |           | 0.019    |             |         |
| <65                  |           | 17.1     |             |         |
| ≥65                  |           | 12.6     |             |         |
| Sex                  |           | 0.93     |             |         |
| Male                 |           | 14.5     |             |         |
| Female               |           | 12.9     |             |         |
| WHO classification   |           | 0.004    | 0.054       |         |
| MDS and low blast count AML | 14.5 |           | 1           |         |
| MDS/MPN              |           | 7.7      | 2.68 (0.98-7.32) | <0.001 |
| French Prognostic Scoring System | <0.0001 |           |             |         |
| Low                  |           | 27.3     | 1           |         |
| Intermediate         |           | 14.5     | 1.92 (1.22-3.01) | 0.0005 |
| High                 |           | 9.9      | 3.83 (2.14-6.88) | <0.001 |
| Response to AZA      |           | <0.0001  |             |         |
| CR+CR+PR             |           | 27.6     | 1           |         |
| HI or SD             |           | 14.0     | 2.20 (1.53-3.15) | <0.0001 |
| Failure              |           | 7.6      | 4.44 (2.98-6.62) | <0.0001 |

HR: Hazard ratio; 95% CI: 95% Confidence Intervals.
Supplementary Table 2. Multivariate analysis of prognostic factors for overall survival after AZA failure in patients with available post-HMA score (n=198; 194 with full data).

| Univariate analysis | Multivariate analysis |
|---------------------|-----------------------|
|                      | Median OS after AZA failure | p-value | HR (95% CI) | p-value |
| Sex                 |                          | 0.58    |             |         |
| Male                |                          | 6.1     |             |         |
| Female              |                          | 4.9     |             |         |
| WHO classification  |                          | 0.098   |             |         |
| MDS and low blast count AML |                      | 5.9     |             |         |
| MDS/MPN             |                          | 2.8     |             |         |
| Post-HMA Score      |                          | 0.0006  | 0.001       |         |
| Low                 |                          | 8.3     | 1           |         |
| High                |                          | 4.8     | 1.76 (1.27-2.45) | 0.001 |
| Response to AZA     |                          | 0.071   |             |         |
| CR                  |                          | 8.4     |             |         |
| HI or SD            |                          | 6.0     |             |         |
| Failure             |                          | 2.9     |             |         |

HR: Hazard ratio; 95% CI: 95% Confidence Intervals.

Supplementary Table 3. Multivariate analysis of prognostic factors for overall survival after loss of the initial response to AZA (n=82; 67 with full data).

| Univariate analysis | Multivariate analysis |
|---------------------|-----------------------|
|                      | Median OS after AZA failure | p-value | HR (95% CI) | p-value |
| Sex                 |                          | 0.32    |             |         |
| Male                |                          | 7.9     |             |         |
| Female              |                          | 4.9     |             |         |
| WHO classification  |                          | 0.28    |             |         |
| Low blast count AML |                          | 6.7     |             |         |
| MDS                 |                          | 14.9    |             |         |
| Post-HMA Score      |                          | 0.032   | 0.04        |         |
| Low                 |                          | 9.2     | 1           |         |
| High                |                          | 5.6     | 1.75 (1.03-2.97) | 0.04 |
| Immediate AZA withdrawal after loss of response | | 0.027 | 0.02         | |
| Yes                 |                          | 4.6     | 1           |         |
| No                  |                          | 8.0     | 1.85 (1.10-3.11) | 0.02 |

HR: Hazard ratio; 95% CI: 95% Confidence Intervals.
### Supplementary Table 4. Clinical information of 82 patients who relapsed after an initial response to azacytidine.

| Parameters (median, range) | (Immediately stopped AZA, n=37) | (Continued AZA, n=45) | p-value |
|---------------------------|----------------------------------|-----------------------|---------|
| Age at relapse             | 73 (51.4-82.3)                  | 73 (50.1-83.1)        | 0.59    |
| Sex                       |                                  |                       | 0.5     |
| Male                      | 25 (67.5%)                      | 27 (60%)              |         |
| Female                    | 12 (32.5%)                      | 18 (40%)              |         |
| WHO classification at relapse |                                |                       | 0.6     |
| RCMD                      | 0 (0%)                          | 2 (4.4%)              |         |
| RAEB-I                    | 3 (8.1%)                        | 3 (6.6%)              |         |
| RAEB-II                   | 10 (27%)                        | 11 (24.5%)            |         |
| Low blast count AML       | 14 (37.9%)                      | 14 (31.1%)            |         |
| N/A                       | 10 (27%)                        | 15 (33.4%)            |         |
| IPSS at diagnosis         |                                  |                       | 0.36    |
| Low/Intermediate-1        | 7 (19%)                         | 6 (13.3%)             |         |
| Intermediate-2            | 13 (35.1%)                      | 24 (53.3%)            |         |
| High                      | 13 (35.1%)                      | 13 (28.9%)            |         |
| N/A                       | 4 (10.8%)                       | 2 (4.5%)              |         |
| IPSS-R at diagnosis       |                                  |                       | 0.93    |
| Low                       | 2 (5.4%)                        | 2 (4.5%)              |         |
| Intermediate              | 5 (13.5%)                       | 5 (11.1%)             |         |
| High                      | 15 (40.6%)                      | 19 (42.2%)            |         |
| Very high                 | 11 (29.7%)                      | 17 (37.7%)            |         |
| N/A                       | 4 (10.8%)                       | 2 (4.5%)              |         |
| FPSS (GFM) at diagnosis   |                                  |                       | 0.76    |
| Low                       | 6 (16.2%)                       | 5 (11.1%)             |         |
| Intermediate              | 21 (56.8%)                      | 28 (62.2%)            |         |
| High                      | 5 (13.5%)                       | 7 (15.6%)             |         |
| N/A                       | 5 (13.5%)                       | 5 (11.1%)             |         |
| Post HMA model            |                                  |                       | 0.45    |
| Low                       | 10 (27%)                        | 17 (37.7%)            |         |
| High                      | 19 (51.3%)                      | 22 (49%)              |         |
| N/A                       | 8 (21.7%)                       | 6 (13.3%)             |         |
| Treatment after AZA       |                                  |                       | 0.61    |
| discontinuation           |                                 |                       |         |
| Supportive care           | 16 (43.3%)                      | 20 (44.4%)            |         |
| Intensive chemo           | 10 (27%)                        | 8 (17.6%)             |         |
| Low intensity chemo       | 1 (2.7%)                        | 1 (2.2%)              |         |
| Decitabine                | 5 (13.5%)                       | 2 (4.4%)              |         |
| Allo-BMT                  | 4 (10.8%)                       | 3 (6.6%)              |         |
| N/A                       | 1 (2.7%)                        | 11 (20.7%)            |         |
| Number of completed cycles|                                  |                       | 0.17    |
| Median (range)            | 9 (2-30)                        | 13 (4-59)             |         |
| Red cell transfusion      |                                  |                       | 0.28    |
| dependency at diagnosis   |                                 |                       |         |
| Yes                       | 23 (62.1%)                      | 33 (73.4%)            |         |
| No                        | 12 (32.4%)                      | 10 (22.2%)            |         |
| N/A                       | 2 (5.5%)                        | 2 (4.4%)              |         |

**Abbreviations:** IPSS = International Prognostic Scoring System, IPSS-R = revised International Prognostic Scoring System, WPSS = World Health Organization classification-based Prognostic Scoring System, FPSS = French Prognostic Scoring System, RCMD = refractory cytopenia with multilineage dysplasia, RAEB = refractory anemia with excess blasts, AML = acute myeloid leukemia, N/A = not available/applicable.