Myelodysplastic Syndromes

Latency of onset of de novo myelodysplastic syndromes

The latency of onset of de novo myelodysplastic syndromes (MDS) is unknown. We report a retrospective analysis of blood counts from patients with MDS and acute myeloid leukemia (AML), and demonstrate temporal differences in rates of change of haemoglobin concentration and mean cell volume within 2-3 years of diagnosis, indicative of the earliest evidence of disease.

References

### Letters to the Editor

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**Figure 1A.** Hemoglobin concentration changes prior to date of diagnosis. Crosses represent all values (n=697) for all patients (n= 54). Bold lines represent the best fit either side of a threshold (change point), indicated by the intersection of both lines.

**Figure 1B.** Mean cell volume changes prior to date of diagnosis. Crosses represent all values (n=573) for all patients (n= 50). Bold lines represent the best fit either side of a threshold (change point), indicated by the intersection of both lines.

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disease was not documented. The study was approved by the Tayside Committee for Medical Research Ethics, and written consent obtained from all live patients. We analyzed data from 54 patients (31 female, 23 male) in whom 5 or more blood counts were available, at least 1000 days prior to diagnosis (denoted as -1000 days). French-American British subtypes were: refractory anemia (RA) = 16; RA with ring sideroblasts = 7; RA with excess blasts (RAEB) = 10, chronic myelomonocytic leukemia = 8, RAEB-t/AML = 13. Automated analysis of hemoglobin concentration and red cell indices was available from 1973, subject to internal quality assurance (QA) throughout, and external QA from 1990. The statistical analysis was based on a change point model with two straight lines having 4 unknowns: the change point time, an average level at this time and two rates of change, before and after the change point. Standard errors (SE) were obtained by bootstrapping the fitted model residuals and taking the 10% winsorised standard deviation of the bootstrap distribution.

Median age was 75 years (range 40-95) and the median number of data points per patient was 9 (range 5-67) for haemoglobin concentration (Hb), and 8 (range 5-36) for mean cell volume (MCV). Hb (n=697 data points) showed a probable slow fall, initially of 0.035 g/dL/year (SE 0.016) and latterly of 0.86 g/dL/year (SE 0.12) with a change point at -1025 days (SE 140) (Figure 1A). Hb declined considerably faster for males than females prior to the change point (0.21 g/dL/yr vs. 0.011 g/dL/yr). MCV (n=573 data points) showed a steady rise, initially of 0.42 fl/year (SE 0.09) and latterly of 3.7 fl/year (SE 1.5), with a change point at -625 days (SE 205) (Figure 1B). Median Hb and MCV at the change point were 12.4 g/dL (SE 0.2) and 95.2 fl (SE 0.9) respectively, and at diagnosis were 9.5 g/dL (SE 0.21) and 102 fl (SE 1.3) respectively. Platelets (n=915 data points) tended to decrease at -7×10^11/L/yr (SE 1.0), and monocytes (n=784 data points) to increase at 0.035×10^11/L/yr (SE 0.0080), but with no clear evidence for change points. Neutrophils remained relatively constant throughout. Insufficient data were available for meaningful analysis of individual FAB subgroups. This is the first systematic attempt to study the latency of onset of de novo MDS/AML. We recognize the limitations of our retrospective study, including the influence of co-existing disease and medication, the often arbitrary date that a diagnosis of MDS is made, and restrictions of small sample size for meaningful analysis of MDS/AML sub-groups. Nevertheless, the direction of change for each parameter (increase or decrease) is as would be expected. The slower phase of change (before the change point) for Hb and MCV may represent a physiological age-related process, comparable in magnitude to that in two previous cohort studies from similar aged, healthy populations in Japan and Sweden, and similarly greater for males than females. The faster phase of change (after the change point), occurring within 2-3 years prior to the date of diagnosis, more likely represents the earliest clinical erythroid manifestation of haematological disease. The presence of a change point for both red cell parameters (Hb and MCV), not observed for neutrophils, monocytes or platelets is consistent with a more prevalent erythroid than non-erythroid defect in MDS at diagnosis. White cell parameters were not studied in the healthy Swedish or Japanese cohorts. We consider that a progressive increase in monocytes and decrease in platelets is likely to represent developing hematologic disease. Our data suggest the onset of hematologically detectable de novo MDS/AML at least 2-3 years prior to the presentation of overt clinical disease. The more protracted evolutionary phase for monocytes and platelets indicate that this latent pre-clinical phase may be considerably longer. The length of time from the first hematopoietic stem cell insult to the development of laboratory changes in blood counts remains unknown.
Chronic Myeloproliferative Disorders

Anagrelide-associated cardiomyopathy in polycythemia vera and essential thrombocythemia

A comprehensive database inquiry at our institutions identified 11 patients with echocardiogram-documented idiopathic cardiomyopathy that post-dated a diagnosis of either polycythemia vera or essential thrombocythemia. Anagrelide therapy was temporally associated with the particular complication in 6 patients, all of whom experienced symptomatic and/or objective improvement after drug discontinuation.

Anagrelide, an oral imidazoquinazoline derivative, effectively lowers platelet count in a spectrum of chronic myeloproliferative disorders, including essential thrombocythemia (ET) and polycythemia vera (PV), with a proposed mechanism of action that involves interference with megakaryocyte differentiation.1,2 Previously reported side effects of anagrelide have included headache, palpitations, diarrhea, fluid retention and abdominal pain, nausea, dyspepsia, and rash. In addition, anecdotal reports of idiopathic congestive heart failure in patients receiving anagrelide therapy have surfaced but have not been formally studied.3

In a retrospective, IRB-approved study, the Mayo Clinic Rochester database was queried and cross-referenced for diagnoses of cardiomyopathy or heart failure and polycythemia, thrombocythsis, or thrombocythemia. The initial inquiry yielded 434 cases, which were thoroughly reviewed to confirm the diagnosis of either PV or ET as well as to identify patients with an echocardiogram-documented idiopathic cardiomyopathy (ICM) that post-dated the hematologic diagnosis. A diagnosis of ICM required echocardiogram documentation of a reduced left ventricular systolic ejection fraction (EF < 50%) as well as the absence of both coronary artery disease and other causes of cardiomyopathy. Once a temporal association between anagrelide therapy and ICM was recognized during the initial phase of the study, the Mayo Clinic Jacksonville database was subsequently queried and cross-referenced for diagnoses of congestive, heart, and anagrelide.

The database search from the two Mayo Clinic centers resulted in the identification of 11 patients (9 females; age range 46–78 years; 7 PV and 4 ET) with echocardiogram-confirmed ICM that was recognized after the diagnosis of PV/ET at a median period of 9 years (range, 0.5–20). Anagrelide therapy, at standard doses with a median daily dose of 2 mg/day, was temporally associated with ICM in 6 of the 11 patients (4 from Mayo Clinic Rochester and 2 from Mayo Clinic, Jacksonville), all of whom were women and ranged in age from 33 to 77 years (Table 1).

Case #1 had a baseline EF of 69% one year before disease diagnosis. One year after anagrelide had been initiated, an EF of 60% was documented. Four years later, still on anagrelide therapy, the patient developed progressive dyspnea and palpitations and another trans-thoracic echocardiogram (TTE) revealed an EF of 30%. Anagrelide treatment was continued while the patient’s symptoms progressed over the next two months and the EF further declined to 18%. Anagrelide was stopped at that point and four months later the patient’s symptoms as well as the EF (25%) improved. Sixteen months after the diagnosis of ICM, the patient’s EF remains abnormal at 28%.

Case #2 was treated with anagrelide for 6 months before experiencing acute onset congestive heart failure. TTE showed an EF of 25%. Upon cessation of anagrelide, the patient’s symptoms improved.

Case #3 was on anagrelide therapy for just over three years when she developed fatigue and dyspnea on exertion; TTE showed an EF of 20%. Anagrelide was immediately discontinued, her symptoms improved and follow-up TTE one year later showed dramatic improvement of her EF to 66%.

Table 1. Clinical and echocardiogram information in six patients, all females, with anagrelide-associated cardiomyopathy.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Diagnosis</th>
<th>Interval (months)</th>
<th>Diagnosis to ICM</th>
<th>Anagrelide treatment to ICM</th>
<th>Before treatment</th>
<th>Ejection fraction (%)</th>
<th>Off-anagrelide therapy for 0.2-16 months</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>PV</td>
<td>66</td>
<td>60</td>
<td>69</td>
<td>30 and then 18 on continued anagrelide treatment</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ET</td>
<td>8</td>
<td>6</td>
<td>NA</td>
<td>25</td>
<td>NA</td>
<td></td>
</tr>
<tr>
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<td>PV</td>
<td>120</td>
<td>36</td>
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<td>20</td>
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<td></td>
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<tr>
<td>4</td>
<td>PV</td>
<td>156</td>
<td>13</td>
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<tr>
<td>5</td>
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<td>ET</td>
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<td>10</td>
<td>34</td>
<td></td>
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</tbody>
</table>

ICM, idiopathic cardiomyopathy; Pt, patient; NA, not available.

References
3. Herman N, Rudolf J, Sten L, Alvar S. Blood haemoglobin declines in relation to age from 33 to 77 years; 7 PV and 4 ET with echocardiogram-confirmed ICM that was recognized after the diagnosis of PV/ET at a median period of 9 years (range, 0.5–20). Anagrelide therapy, at standard doses with a median daily dose of 2 mg/day, was temporally associated with ICM in 6 of the 11 patients (4 from Mayo Clinic Rochester and 2 from Mayo Clinic, Jacksonville), all of whom were women and ranged in age from 33 to 77 years (Table 1).