Chronic myeloproliferative disorders: prognostic importance of new working classification

R Burkhardt, K Jaeger, G Kettner, G Helmer

Abstract

Variants of chronic myeloproliferative disorders (CMPD) were compared according to their clinical features and classified by bone marrow biopsy appearances. Subsequently, this classification was further evaluated using survival data and histological variables from iliac crest biopsy specimens of an additional 1391 patients, making a total of 2241 patients available for analysis of outcome. The patients were grouped again into three main classes: "typical"; "variant"; and "transformed". "Typical" comprised the "classic" groups. "Variant" included the less uniform myeloproliferative syndromes, distinguished also by more variable clinical features, a different prognosis, and a greater tendency to fibrotic and blastic transformation. "Transformed" defined the end stages of both "typical" and "variant" types. Ten subgroups were distinguished by different histology and prognosis. Particular prognostic importance was assigned to atypia and immaturity of haemopoiesis, predominance of individual haemopoietic cell line, number and anomalies of megakaryocytes and progressive fibrosis.

It is suggested that the proposed subclassification would be helpful for studies of epidemiology and therapeutic trials by allowing more homogeneous groups to be recognised.

The main groups of chronic myeloproliferative disorders (CMPD), polycythaemia vera, primary thrombocythaemia, and chronic granulocytic leukaemia (CGL)\(^3\)\(^-\)\(^5\) are traditionally classified according to characteristic and at least temporarily constant clinical features, and by exclusion of borderline cases. In practice, however, even the "classic" groups show considerable prognostic inhomogeneity.\(^4\)\(^5\) For example, transformation to the fibrotic or blastic stages is hardly predictable, and several variants often have to be lumped together into ill defined groups—for example, agnogenic myeloid metaplasia,\(^6\) acute myelosclerosis,\(^7\) and blast crisis.\(^8\) In our previous study\(^9\) random biopsy specimens of all untreated patients with CMPD since the year 1960 (including those diagnosed as having "unclassified" CMPD) were analysed by comparing histological and clinical data. The purpose of the present analysis was to test the preliminary results by the use of a greater number of cases and survival data to identify the clinically relevant subgroups (see classification table 1 and revised classification in table 2).

Methods

Iliac crest biopsy specimens from 2241 patients with CMPD (850 untreated and 1391 previously treated) were evaluated by the methodology described in our previous paper,\(^9\) and the time of survival from biopsy until death or date of last contact were recorded. Observation of these patients started in 1960 and ended in 1985; the mean observation period was 45.3 months, with a minimum of one and a maximum of 303 months. Classification followed the previously defined model,\(^9\) although the denominations were made more uniform (table 1).

<table>
<thead>
<tr>
<th>Classes</th>
<th>Main groups</th>
<th>Subtypes</th>
<th>Sample size/n</th>
<th>Mean age (years)</th>
<th>Median survival time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Typical</td>
<td>Erythrocytic myelosis (Ery-M) corresponding to polycythaemia vera</td>
<td>EryGranMeg-M</td>
<td>358</td>
<td>55.9</td>
<td>132.1 ± 4.2</td>
</tr>
<tr>
<td></td>
<td>Megakaryocytic myelosis corresponding to primary thrombocythaemia</td>
<td>Ery-M</td>
<td>21</td>
<td>58.1</td>
<td>72.7 ± 4.9</td>
</tr>
<tr>
<td></td>
<td>Granulocytic myelosis (Gran-M) corresponding to CGL</td>
<td>Ery-Md (Meg-diffuse)</td>
<td>148</td>
<td>59.8</td>
<td>126.9 ± 4.1</td>
</tr>
<tr>
<td></td>
<td>Gran-M-c (Meg-clustered)</td>
<td>Ery-Mc (Meg-clustered)</td>
<td>75</td>
<td>62.1</td>
<td>115.0 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>Gran-M-Meg +</td>
<td>Gran-M-Meg +</td>
<td>333</td>
<td>54.8</td>
<td>28.5 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>Gran-M-Meg -</td>
<td>Gran-M-Meg -</td>
<td>66</td>
<td>48.2</td>
<td>21.1 ± 7.7</td>
</tr>
<tr>
<td>II Variant</td>
<td>Erythrocytic myelosis variants corresponding to borderline polycythaemia vera-primary thrombocytopenia</td>
<td>Ery-M</td>
<td>166</td>
<td>57.9</td>
<td>108.4 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>Megakaryocytic myelosis variants corresponding to borderline primary thrombocythaemia or cytopenia</td>
<td>EryGran-M</td>
<td>80</td>
<td>62.9</td>
<td>57.0 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Granulocytic megakaryocytic myelosis corresponding to borderline CGL-primary thrombocytopenia</td>
<td>EryGran-M (Meg-immature)</td>
<td>109</td>
<td>55.0</td>
<td>123.3 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>Gran-M-p (Meg-pleomorphic)</td>
<td>EryGran-M-p</td>
<td>18</td>
<td>53.8</td>
<td>6.0 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>GranMeg-M-d (Meg-diffuse)</td>
<td>GranMeg-M-d</td>
<td>209</td>
<td>62.0</td>
<td>64.6 ± 4.1</td>
</tr>
<tr>
<td></td>
<td>GranMeg-M-c (Meg-clustered)</td>
<td>GranMeg-M-c</td>
<td>228</td>
<td>63.3</td>
<td>49.6 ± 5.5</td>
</tr>
<tr>
<td>III Transformed</td>
<td>Osteomyelofibrosis variants corresponding to myeloid metaplasia or cytopenia</td>
<td>OMS (Osteomyelosclerosis)</td>
<td>198</td>
<td>60.8</td>
<td>30.3 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>Blastic osteomyelofibrosis variants similar to malignant myelosclerosis</td>
<td>MF (Myelofibrosis)</td>
<td>48</td>
<td>64.8</td>
<td>15.0 ± 4.3</td>
</tr>
<tr>
<td></td>
<td>Blastic myelosclerosis variants corresponding to blastic crisis</td>
<td>B-OMS</td>
<td>24</td>
<td>59.6</td>
<td>6.5 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>Blastic myelosclerosis variants corresponding to nonblastic crisis</td>
<td>B-MF</td>
<td>64</td>
<td>61.2</td>
<td>3.8 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Blastic myelosclerosis variants corresponding to nonblastic crisis</td>
<td>B-M-mult (multilinear)</td>
<td>43</td>
<td>57.8</td>
<td>10.0 ± 4.3</td>
</tr>
<tr>
<td></td>
<td>Blastic myelosclerosis variants corresponding to nonblastic crisis</td>
<td>B-M-un (unilinear)</td>
<td>53</td>
<td>57.0</td>
<td>4.6 ± 1.5</td>
</tr>
</tbody>
</table>

\(^*\)Horizontal lines between pairs of data indicate that the difference between the respective means is significant at the 0.01% level.
Class I was primarily defined by the accepted criteria (chromosomal analyses were available only in a few cases), and subdivided according to the histological features mentioned above.

Classes II and III were defined by histology alone, with the exception of the PV variants. Pure blastic variants were included only when antecedent CMPD was confirmed; blastic variants combined with typical myelofibrosis or osteomyelosclerosis were generally registered as B-MF or B-OMS, most tracing back to original CMPD. Myelofibrosis and osteomyelosclerosis groups were defined only by those cases in which fibrotic or osteosclerotic changes had already obscured the typical CMPD characteristic. The diagnosis of CMPD was then deduced either from remaining foci of (predominantly megakaryocytic) myeloproliferation or the case history. Cases of CMPD with only minor fibrotic or osteosclerotic changes, including reticular sclerosis, were assigned to their original groups.

Definitions of the various conditions, together with correlations of histological changes with clinical and haematological data, have been given previously. The former concerned the different forms of megakaryocytes (normal, dwarf, giant, immature, and pleomorphic), the proliferation, maturity, and predominance of haemopoietic cell lines, and the conditions of reticular sclerosis, myelofibrosis, and osteomyelosclerosis, as well as the correlations of histological changes with clinical and haematological data. The reliability of the histological data had already been assured by at least two observers and the use of at least five differently stained slides.

The survival periods were correlated with the patients' age and sex, the histological subtypes, and the fibrotic and non-fibrotic changes in the biopsy specimens. The data were analysed using BMDP statistical packages. Differences between groups were tested for significance using the methods of Breslow and Mantel-Cox.

### Table 2 Revised histological classification of CMPD: clinical appearance, age, fibrosis and survival

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical appearance corresponding with</th>
<th>Mean age (years)</th>
<th>Collagenous fibrosis (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong> typical (n = 1001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 Erythrocytic myelosis (Ery–M; EryGranMeg–M)</td>
<td>17% Polycythaemia vera, typical</td>
<td>56-0</td>
<td>3%</td>
<td>128-8</td>
</tr>
<tr>
<td>2 Megakaryocytic myelosis (Meg-M-d; Meg-M-c)</td>
<td>10%</td>
<td>60-5</td>
<td>13%</td>
<td>124-2</td>
</tr>
<tr>
<td>3 Granulocytic myelosis (Gran–M–Meg + – Meg –)</td>
<td>18%</td>
<td>548/48-2</td>
<td>19%/9%</td>
<td>295/21-1</td>
</tr>
<tr>
<td><strong>Class II Variant</strong> (n = 683)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4 Erythrocytic-megakaryocytic myelosis (EryMeg–M)</td>
<td>7% Polycythaemia vera, primary thrombocythaemia, borderline</td>
<td>57-9</td>
<td>37%</td>
<td>94-8</td>
</tr>
<tr>
<td>5 Erythrocytic-granulocytic myelosis (EryGran–M)</td>
<td>3%</td>
<td>62-4</td>
<td>30%</td>
<td>57-0</td>
</tr>
<tr>
<td>6 Granulocytic-megakaryocytic myelosis (GranMeg–M–d; GranMeg–M–c)</td>
<td>20%</td>
<td>62-6</td>
<td>46%</td>
<td>56-8</td>
</tr>
<tr>
<td><strong>Class III Transformed</strong> (n = 557)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 7 Osteomyelosclerosis (OMS)</td>
<td>9% Myeloid metaplasia or cytopenia</td>
<td>60-8</td>
<td>100%</td>
<td>30-3</td>
</tr>
<tr>
<td>8 Myelofibrosis (MF)</td>
<td>2%</td>
<td>64-8</td>
<td>100%</td>
<td>15-0</td>
</tr>
<tr>
<td>9 Blastic myelosis, multiline (B-M–mult; B-OMS; B–MF)</td>
<td></td>
<td>57-5</td>
<td>45%</td>
<td>8-8</td>
</tr>
<tr>
<td>10 Blastic myelosis, unilin (B–M–un)</td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

100% = 2,241 cases

**Abbreviations**

- B-M = blastic myelosis
- B-M-V = blastic myelosis variants
- B-M-un = blastic myelosis unilin
- B-M-mult = blastic myelofibrosis
- B-OMS = blastic osteomyelosclerosis
- CGL = chronic granulocytic leukaemia
- CMPD = chronic myeloproliferative disorder
- Ery–M = erythrocytic myelosis
- Ery–V = erythrocytic myelosis variants
- EryGranMeg–M = erythro-granulo-megakaryocytic myelosis
- EryGran–M = erythro-granulocytic myelosis
- EryMeg–M = erythro-megakaryocytic myelosis
- Gran–M = granulocytic myelosis
- Gran–M–V = granulocytic myelosis variants
- Gran–M–Meg + – Meg – = granulocytic myelosis poor in megakaryocytes
- Gran–M–Meg + = granulocytic myelosis rich in megakaryocytes
- GranMeg–M = granulo-megakaryocytic myelosis
- GranMeg–M–V = granulo-megakaryocytic myelosis variants
- GranMeg–M–d = granulo-megakaryocytic myelosis with diffuse megakaryocytes
- GranMeg–M–c = granulo-megakaryocytic myelosis with clustered megakaryocytes
- Meg–M = megakaryocytic myelosis
- Meg–M–V = megakaryocytic myelosis variants
- Meg–M–d = megakaryocytic myelosis with diffuse megakaryocytes
- Meg–M–c = megakaryocytic myelosis with clustered megakaryocytes
- Meg–M–i = megakaryocytic myelosis with immature megakaryocytes
- Meg–M–p = megakaryocytic myelosis with pleomorphic megakaryocytes
Prognostic classification in chronic myeloproliferation

Figure 1a Erythrocytic myelosis (EryGranMeg-M) corresponding to polycythaemia vera: typical trilineal proliferation with incipient cluster formation of megakaryocytes and slight reticular sclerosis. (Gomori's silver impregnation.)

1b Granulocytic myelosis (Gran-M-Meg+) corresponding to CGL: typical granulocytic proliferation with strong increase in dwarf megakaryocytes; incipient transformation into Meg-M-i? (Gallamin blue-Giemsa stain.)

1c Megakaryocytic myelosis (Meg-M-c) corresponding to primary thrombocythaemia: typical proliferation of giant megakaryocytes among otherwise normal haemopoiesis. (Gallamin blue-Giemsa stain.)

1d Granulo-megakaryocytic myelosis (GranMeg-M-c); granulocytic proliferation together with accumulations of giant megakaryocytes in large clusters. (Gallamin blue-Giemsa stain.)

Results

Sixty-three per cent of the patients had died; thirty-seven per cent were known to be still alive. The longest median survival was 132.1 months (EryGranMeg-M = polycythaemia vera), the shortest 3.8 months (B-MF). The median survivals of patients untreated at the time of biopsy did not differ significantly from those of patients who had already received specific treatment. This applied to all types and subtypes. Moreover, comparative histological evaluation showed no reasons for a separate analysis of treated and untreated patients. The overall ratio between male and female patients was 1.03:1; significant predominance of one sex (female) was found only in mature and immature megakaryocytic myelosis (Meg-M and Meg-M-i).

OVERALL SURVEY (table 1)

The number of patients was higher and the mean age lower in the typical class than in the variant and transformed classes (n = 1001:810:430 patients; mean ages = 56.1:60.4:60.6 years). These figures seem to support the hypothesis that the classes I to III represent sequential stages of CMPD.

Within each class, differences in the median survivals of the main groups were as follows (the symbol > denotes longer than): I: Ery(GranMeg)-M > Gran-M; Meg-M > Gran-M; II: Ery-M-V > Meg-M-i; Gran-M-V > Meg-M-i; III: OMS > B-OMS; OMS > B-M.

Significantly different median survival times were also detected between corresponding pairs of subtypes (different pairs marked...
Figure 2  Life table: survivals for three megakaryocytic subtypes of CMPD; A = (Meg-M) respectively primary thrombocytopenia; B = (GranMeg-M); C = (Meg-M-i).

<table>
<thead>
<tr>
<th>Subtype</th>
<th>n</th>
<th>Mean age (years)</th>
<th>Median survival (months)</th>
<th>Significance tests Breslow</th>
<th>Significance tests Mantel-Cox</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  =  Megakaryocytic myelosis</td>
<td>223</td>
<td>61</td>
<td>128</td>
<td>0.0003</td>
<td>0.0001</td>
</tr>
<tr>
<td>B  =  Granulocytic-megakaryocytic myelosis</td>
<td>437</td>
<td>63</td>
<td>54</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>C  =  Megakaryocytic immature myelosis</td>
<td>127</td>
<td>55</td>
<td>11</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Figure 3a  
Megakaryocytic immature myelosis (Meg-M-i); large sheets of mostly immature megakaryocytes. (Gallamin blue-Giemsa stain.)

3b Myelofibrosis; small groups of immature, partially necrotic megakaryocytes amid fibrotic obliteration of the marrow space. (Gomori's silver impregnation.)

3c Osteomyelosclerosis (OMS); irregular strands of primitive bone, produced by osteoblasts, enclosing islets of haemopoietic bone marrow with numerous giant and necrotic megakaryocytes. (Gallamin blue-Giemsa stain.)

3d Blastic multilinear myelosis (B-M-mult); irregular proliferation of blastic elements of all cell lines, predominantly pleomorphic megakaryoblasts and -cytes, and collagenous fibrosis. (Gallamin blue-Giemsa stain.)
Prognostic classification in chronic myeloproliferation

Figure 4 Life table: survivals for four transformed subtypes of CMPD; A = osteomyelosclerosis (OMS); B = myelofibrosis (MF); C = blastic multilineal myelosis (B-M-mult); D = blastic unilineal myelosis (B-M-un) grouped together with blastic osteomyelosclerosis (B-OMS), and blastic myelofibrosis (B-MF).

COMPARISON OF SURVIVAL TIMES OF SUBTYPES (ACCORDING TO PREDOMINANT CELL LINES)

Erythrocytic predominance
Median survival times of EryGranMeg-M were equal to that of typical polycythaemia vera. Moreover, of the variant subtypes of polycythaemia vera, the survival times for EryMeg-M (fig 1a), differed from those of EryGran-M; p = 0.0001 (Breslow and Mantel-Cox tests). Pure Ery-M comes closer to the variant subtypes in this respect, although the group was too small for statistical evaluation.

Granulocytic predominance
Patients with Meg- subtype of Gran-M showed shorter median survival times than those with Gran-M-Meg+, the latter being equal to that of typical CGL (fig 1b) (p = 0.0001 in both Breslow and Mantel-Cox tests). The latter group also survived for a shorter time than patients with EryGran-M (p = 0.02, Breslow test; and p = 0.004, Mantel-Cox test), and than those with Gran-Meg-M (p = 0.0001, Breslow and Mantel-Cox tests). These variant groups did not differ from each other in this respect.

Figure 5 Life table: correlation of fibrotic changes and survival of 1955 patients with CMPD (including all subtypes except OMS, B-OMS, and B-MF).
Table 3  CMPD subtypes: fibrosis and survival

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Degree of fibrosis</th>
<th>Level of significance for differences in median survivals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None or reticular sclerosis</td>
<td>Collagenous fibrosis</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean age</td>
</tr>
<tr>
<td>Erythrocytic myelosis (EryGranMeg-M)</td>
<td>340</td>
<td>54</td>
</tr>
<tr>
<td>Megakaryocytic myelosis (Meg-M-c)</td>
<td>52</td>
<td>61</td>
</tr>
<tr>
<td>Granulocytic myelosis (Gran-M-Meg +)</td>
<td>270</td>
<td>53</td>
</tr>
<tr>
<td>Erythrocytic megakaryocytic myelosis (EryMeg-M)</td>
<td>105</td>
<td>56</td>
</tr>
<tr>
<td>Granulocytic megakaryocytic myelosis (GranMeg-M-c)</td>
<td>165</td>
<td>62</td>
</tr>
<tr>
<td>Megakaryocytic immature myelosis (Meg-M-i)</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Blastic myelosis</td>
<td>30</td>
<td>60</td>
</tr>
</tbody>
</table>

75th quantile: 55 months = more than 50% of patients alive during control time.

**Megakaryocytic predominance**

Here the differences in median survival times in the subtypes are most noteworthy, as can be observed from the life table in fig 2: Meg-M (fig 1c) > GranMeg-M > Meg-M-i (fig 3a).

**Transformation**

The transformed fibrotic and blastic variants are compared in the life table (fig 4), and in figs 3b–d. Life expectancy decreased in the following order: OMS > MF > B-M-mult > B-OMS and B-M-un.

**Correlation between fibrosis, age, and survival**

There were only 130 cases (with a mean age of 55 years) in which no fibrotic changes were evident at all; most (n = 1289 with a mean age 57 years) exhibited reticular sclerosis; 468 (mean age 61 years) presented focal to moderate degrees of collagenous fibrosis; osteomyelosclerosis was diagnosed in 198 patients (mean age 60.8 years), and myelofibrosis in 48 patients (mean age 64.8 years). Fibrosis was in general associated with a worse prognosis (fig 5).

On the other hand, increasing age diminishes the life expectancy in chronic disorders, and especially in CMPD: 807 of the patients with a mean age of 42 years had a median survival of 74 months, against 55 months for a mean age of 62 years (n = 726); p = 0.02 Breslow, p = 0.0007 Mantel-Cox, and 27 months for mean age of 73 years (n = 688). These differences were also significant (p = 0.0001, Breslow and Mantel-Cox). There was, however, a pronounced tendency for fibrosis among the subtypes: thus fibrosis was most frequently absent in Meg-M-d; reticular sclerosis was most common in Ery(Gran-Meg)-M and Gran-M; and collagenous fibrosis was very evident in the clustered subtypes of Meg-M and GranMeg-M and in Meg-M-i.

The significant correlations between the median survival times and fibrotic changes on the one hand, and age on the other, were both positive in most groups (tables 3 and 4). Statistical congruence (using the χ² test) between age and degree of fibrosis, however, was manifest in only two subtypes—namely, Gran-M-Meg + and EryMeg-M. These variables diverged considerably from one another in Meg-M-i, myelofibrosis and B-M-mult, in which the detrimental influence of fibrosis dominated, and in GranMeg-M-d, in which age, not degree of fibrosis, was the major indicator of poorer life expectancy.

**Revised prognostic classification**

As a result of the above findings, it was necessary to revise our previous scheme of prognostic classification as follows (table 2): 10 groups of CMPD were distinguished primarily by their histology and prognosis and assigned to three classes:

- **Class I** ("typical") was characterised by the uniform connection between the well known histological changes and clinical symptoms with a moderate tendency to transformation.
- **Class II** ("variant") was defined by the less uniform proliferation of more than one cell

Table 4  CMPD subtypes: age and survival

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Age</th>
<th>Level of significance for differences in median survivals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger patients</td>
<td>Older patients</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean age</td>
</tr>
<tr>
<td>Erythrocytic myelosis (EryGranMeg-M)</td>
<td>183</td>
<td>46</td>
</tr>
<tr>
<td>Megakaryocytic myelosis (Meg-M-c)</td>
<td>73</td>
<td>49</td>
</tr>
<tr>
<td>Granulocytic myelosis (Gran-M-Meg +)</td>
<td>168</td>
<td>41</td>
</tr>
<tr>
<td>Erythrocytic megakaryocytic myelosis (EryMeg-M)</td>
<td>87</td>
<td>48</td>
</tr>
<tr>
<td>Granulocytic megakaryocytic myelosis (GranMeg-M-c)</td>
<td>111</td>
<td>52</td>
</tr>
<tr>
<td>Granulocytic megakaryocytic myelosis (GranMeg-M-d)</td>
<td>123</td>
<td>56</td>
</tr>
<tr>
<td>Osteomyelosclerosis (OMS)</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
<td>Myelofibrosis (MF)</td>
<td>25</td>
<td>57</td>
</tr>
</tbody>
</table>

*75th quantile: 55 months = more than 50% of patients alive during control time.
line with intermediate clinical symp-
tomatology (compared with the "classic"
groups), and noticeable instability.

Class III ("transformed") comprised the fully
developed fibrotic or blastic variants of I and
II, and a small subgroup of possibly
"primary" osteomyelosclerosis and
myelofibrosis with a (sub)chronic course. The
secondary origin and acute to subacute course
of the immature and pleomorphic megakary-
cytic myeloses resembles the "blastic
crises" of other haemopoietic cell lines. As
they are generally combined with multinuclear
haemopoietic proliferation and have a strong
tendency to fibrosis, they were integrated into
group 9. Collagenous fibrosis in class I varies
from 5-19%, in class II from 30-46%, and in
class III from 17-100% of the cases.

Discussion

The detection of the clonal origin of CMPD has
contribution to our understanding of its
diversity of phenotypes and transformations,
which by far exceeds the accepted standards.
Moreover, we are beginning to understand
some of the consequences of uncontrolled
myeloproliferation for the local organisation
of cellular production and release, such as
the fibroblastic sequelae of excess megakaryocytosis. It is now also evident
that cell line specific symptoms of CMPD
have different influences on the time and
mode of the final collapse. In the light of these
findings the total spectrum of CMPD was
analysed primarily from the aspect of the
structural pathogenesis at the site of its origin,
the bone marrow. This attempt was supported by
a 25 year database of technically uniform
iliac crest biopsy specimens including case
controls, clinical findings, and survival data.
Biopsy specimens of previously treated
patients were included, because treated and
untreated groups did not differ significantly
from each other, as has also been found by
other authors.

Class I adds a more precise histological
scale to the well defined diagnostic criteria of
the typical CMPD groups. It becomes clear
that isolated proliferation of every
haemopoietic cell line has its characteristic
prognosis, provided that release of the mature
cells into the blood is unimpaired: the most
inert form of proliferation is megakaryocytic,
followed by erythrocytic, and ultimately gran-
ulocytic proliferation as the most unfavoura-
ble. Erythrocytic-erythroblast proliferation,
however, is rare and its association with
polycythaemia vera dubious. In accordance
with published findings, the life expect-
ancy of the trilinear proliferation of polycyth-
ema vera was found to surpass the rest of
CMPD, possibly due to its proximity to
healthy bone marrow activity. The consistent
longevity of Meg-M contrasts with some
previous data which might be due to bias as
a result of the inclusion of thrombocythemic
cases belonging to other subgroups. The con-
siderable reported variation in survivals of
patients could have been caused
by the different life expectancies of the Gran-
M-Meg+ and -Meg- subgroups, and the
previously neglected identification of
GranMeg-M, more correctly classified
under group 6. This group is also known as
"chronic megakaryocytic-granulocytic myelosis
(CMGM)", and included considerable num-
bers of Ph1 positive cases. Prognostic impor-
tance has also been attributed to dysplasia and
immaturity of haemopoiesis in CGL. Such
cases were excluded from our Gran-M
groups. The more malignant course of the
esosinophilic variants and their tendency to
rapid fibrosis and immature megakaryocytosis
have been evaluated previously.

Class II variants are characterised by their
comparatively uniform prognosis (by which
the class differs significantly from the others),
the higher proportions of fibrotic cases, and
by the ambivalent cellularity of the blood.
Groups 4 and 5 are regarded as variants of
polycythaemia vera; group 6 resembles CGL
histologically, but may be distinguished
clearly from it by megakaryocytosis of the
giant and not the dwarf type. Groups 4 and 5
are generally preceded by polycythaemia vera;
whereas group 6 may develop de novo or from
groups 2 and 3. A further reason for the
 distinction of the variant groups is their
different tendency to blastic or fibrotic trans-
formation.

Class III comprises the transformed
variants, understood as the naturally irrevers-
bile final stages of the other subgroups. Myelofibrosis, however, may develop into
osteomyelosclerosis; both may acquire blastic
differentiation; and blastic forms may
become fibrotic. The distinction of
myelofibrosis from osteomyelosclerosis,
requiring a biopsy specimen of ample size, is
important not only in view of the different
prognosis, but also in terms of different
pathogenesis. Osteomyelosclerosis can no lon-
ger be regarded merely as the more advanced
stage of myelofibrosis. It may proceed
together with myelofibrosis from the very
beginning, or it may never develop during
the course of myelofibrosis, or it may take a
slower course of its own, possibly triggered
by a specific (as yet unknown) osteoblast-
activating factor.

Common presages of myelofibrosis and
osteomyelosclerosis are the clustered foci of
megakaryocytes, observed mostly in groups 1,
2, and 6. These early signs of inefficient
megakaryocytosis are followed by the
accompanying accumulations of necrotic
megakaryocytes and dislocated platelets.
Their detrimental effects are most con-
picuous when held up against the good prog-
nosis of diffuse megakaryocytosis with safe
release of excess platelets. Common presages
of unilinear granulocytic blastosis and of
immature, pleomorphic, or blastic me-

-karyocytosis are groups 3 and 5. Additional
studies are required to evaluate the prognosis
of the individual cell line forming the B-M-un
group. Erythroid and megakaryoblastic crises
generally involve more than one cell line and
tend to develop into progressive fibrosis; they
are both classified into group 9 because of similar prognosis and treatment, but are differentiated from unilinear blastic crises (group 10). Primary "acute myelosclerosis" is not distinguished by histology from group 9.

The overall survey of CMFD shows that the course of the disorder depends primarily on the degree of cellular differentiation and the type of the cell lines involved, but much more on the former. Additionally, the involvement of one or more cell lines in itself is a valuable indicator for diagnosis and prognosis. Further prognostic factors are fibrosis and age.

The rigid definition of myelofibrosis and osteomyelosclerosis results in shorter survivals for these groups and allows us to analyse the prognostic influence of minor degrees of fibrosis in the other subtypes. In this way it became evident that reticular fibrosis is not correlated with later osteomyelosclerosis and myelofibrosis, while collagenous fibrosis from its initial focal stages indicates progressive fibrosis. The different prognostic role of fibrosis and age in the subgroups is another argument for the meticulous histological analysis of CMFD. Moreover, it is important to know that this very common procedure has substantial diagnostic and prognostic value of its own.

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Chronic myeloproliferative disorders: prognostic importance of new working classification.
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