Chronic neutrophilic leukaemia: 14 new cases of an uncommon myeloproliferative disease

J Böhm, H E Schaefer

Background: Chronic neutrophilic leukaemia (CNL) is a rare BCR/ABL negative myeloproliferative disorder characterised by persistent neutrophilia and splenomegaly. Most patients with CNL have a poor prognosis, with a mean survival time of 21 months. To date, only 129 cases of CNL have been reported in the literature.

Aims: To report the findings from a large group of 14 new cases of CNL, consisting of eight women and six men (mean age, 64.7 years).

Methods: A review of the 14 new cases of CNL and the investigation of BCR/ABL translocations in these patients.

Results: Three quarters of the patients died within two years after diagnosis, mostly as a result of severe cerebral haemorrhage. Two patients were successfully treated with allogeneic bone marrow transplantation or interferon, which resulted in haematological remission for periods of up to 41 months.

Conclusion: CNL is a rare myeloproliferative disease mostly taking a fatal clinical course, despite the presence of mature neutrophils as leukaemic cells in the blood. Thus, it is important to recognise CNL to develop appropriate therapeutic strategies for affected patients.

DISCUSSION

The main diagnostic criteria of CNL are chronic neutrophilic leukaemia in the blood, expansion of neutrophilic granulopoiesis in the bone marrow, and splenomegaly in the absence of any form of BCR/ABL translocation or leukaemoid reaction. These criteria were sufficiently fulfilled in our 14 patients with CNL. However, the spectrum of fatal complications we saw in our patients was very similar to that described in the literature. The haemorrhagic diathesis seen in patients with CNL may be the result of thrombocytopenia and thrombocyte dysfunction, or it may be caused by leukaemic infiltration of vascular walls. With rare exceptions, CNL is a disease of older adults (fig 1). At the time of diagnosis, 88% of the patients with CNL in the literature were older than 50 years. The sex distribution in CNL is nearly equal.

There is doubt about whether all of the CNL cases in the literature represent true CNL. Some authors have suggested

Abbreviations: CML, chronic myeloid leukaemia; CNL, chronic neutrophilic leukaemia; NAP, neutrophil alkaline phosphatase
that those cases of CNL that occurred in association with plasma cell dyscrasias like myeloma were in fact neutrophilic reactions. Moreover, it was suggested that cases of CNL showing dysplastic features would be better classified as a myelodysplastic entity. Thus, reviewing the data of all CNL cases in the literature, Reilly defined a group of 33 cases of true CNL, including one unpublished case of his own. This group of 33 selected patients with CNL also showed a high mean age (62.5 years) and short survival times (mean survival, 30 months), but had a 2 : 1 male to female ratio. The term true CNL used by Reilly reveals the need for an even more precise definition of CNL as an entity. Thus, the diagnostic criteria of CNL should be applied in a strict manner, especially for the conditions mentioned above.

“In the differential diagnosis of CNL, patients with CML usually show a higher degree of leucocytosis (white blood cell count, ∼ 170 × 10⁹/litre), with more immature granulopoietic forms, a decreased NAP score, and basophilia. In the bone marrow, granulopoiesis is far more left shifted, and micromegakaryocytes are present. The most important criterion of CML is the presence of a BCR/ABL translocation. There is a rare form of CML (neutrophilic chronic myeloid leukaemia) that shares some of the morphological features of CNL, but is characterised by an uncommon type of BCR/ABL translocation (BCR e19/ABL a2). Like CNL, leukaemoid reactions are BCR/ABL negative and show identical morphological changes, including raised NAP scores, making a distinction difficult or even impossible. Because CNL is a clonal disorder, clonality studies of the neutrophils in the future may help to distinguish between cells of leukemic or reactive origin.

To date, because of the rarity of the disease, no therapeutic standard has been determined in chronic neutrophilic leukaemia.”

Table 1  The Freiburg cases of chronic neutrophilic leukaemia, arranged in chronological order

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>BCR/ABL-status</th>
<th>WBC (×10⁹/l)</th>
<th>% N</th>
<th>Hb (g/l)</th>
<th>Plt. (×10³)</th>
<th>F-Up (months)</th>
<th>SpM</th>
<th>NAP</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>40</td>
<td>Negative</td>
<td>22.6</td>
<td>84</td>
<td>129</td>
<td>106</td>
<td>73*</td>
<td>298</td>
<td>BMT, CR</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>69</td>
<td>Negative</td>
<td>34.4</td>
<td>68</td>
<td>117</td>
<td>105</td>
<td>14† (+)</td>
<td>Ni</td>
<td>Chloroma</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>69</td>
<td>Negative</td>
<td>11.3</td>
<td>72</td>
<td>79</td>
<td>117</td>
<td>9† (+)</td>
<td>Ni</td>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>69</td>
<td>Negative</td>
<td>49.2</td>
<td>88</td>
<td>90</td>
<td>84</td>
<td>19† (+)</td>
<td>2</td>
<td>Cerebral haemorrhage</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>77</td>
<td>Negative</td>
<td>89.0</td>
<td>95</td>
<td>102</td>
<td>135</td>
<td>15† (+)</td>
<td>91</td>
<td>Chloroma</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>64</td>
<td>Negative</td>
<td>41.7</td>
<td>84</td>
<td>109</td>
<td>281</td>
<td>9† (+)</td>
<td>55</td>
<td>Cerebral haemorrhage</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>77</td>
<td>Negative</td>
<td>93.0</td>
<td>74</td>
<td>77</td>
<td>116</td>
<td>8† (+)</td>
<td>293</td>
<td>Cerebral haemorrhage</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>81</td>
<td>Negative</td>
<td>35.0</td>
<td>95</td>
<td>108</td>
<td>189</td>
<td>38† (+)</td>
<td>270</td>
<td>Cerebral haemorrhage</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>37</td>
<td>Negative</td>
<td>36.2</td>
<td>92</td>
<td>143</td>
<td>273</td>
<td>41† (+)</td>
<td>383</td>
<td>IFNα</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>72</td>
<td>Negative</td>
<td>38.0</td>
<td>90</td>
<td>89</td>
<td>47</td>
<td>23† (+)</td>
<td>low Blast crisis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>64</td>
<td>Negative</td>
<td>109.0</td>
<td>87</td>
<td>113</td>
<td>161</td>
<td>10† (+)</td>
<td>364</td>
<td>Cerebral haemorrhage</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>52</td>
<td>Negative</td>
<td>30.0</td>
<td>82</td>
<td>140</td>
<td>182</td>
<td>16† (+)</td>
<td>310</td>
<td>No treatment</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>72</td>
<td>Negative</td>
<td>22.8</td>
<td>88</td>
<td>93</td>
<td>62</td>
<td>2† (+)</td>
<td>40</td>
<td>Cerebral haemorrhage</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>63</td>
<td>Negative</td>
<td>24.6</td>
<td>78</td>
<td>123</td>
<td>210</td>
<td>5† (+)</td>
<td>46</td>
<td>No treatment</td>
<td></td>
</tr>
</tbody>
</table>

In patients 2–8, 10, 11 and 13 the outcome was fatal. Haematological data are those found at the time of diagnosis. *, indicates that the patient is alive and the number indicates the number of months since diagnosis; †, indicates that the patient is dead and the number indicates the number of months after diagnosis.

BMT, bone marrow transplantation; CR, complete remission; F-Up, follow up period; Hb, haemoglobin; IFNα, interferon α; %N, % of neutrophils; NAP, neutrophil alkaline phosphatase score (normal range, 20–120); Ni, not investigated; Plt., platelet count; SpM, splenomegaly; WBC, leucocyte count; (+), mild form.

Figure 1  Distribution of patients with chronic neutrophilic leukaemia in the literature (including the Freiburg cases) according to sex and age.
agents, such as hydroxyurea, may temporarily control leucocytosis and splenomegaly, and the use of interferon α may induce long standing clinical remission. So far, allogeneic bone marrow transplantation represents the only treatment modality with curative potential.

We conclude that it is important to recognise CNL as a rare, but distinct, disease entity different from CML, and in particular to distinguish CNL from leukaemoid reactions, because patients with CNL generally have a poor prognosis. To gain a better understanding of the nature of true CNL the reporting of new cases must be encouraged.

**Take home messages**

- Chronic neutrophilic leukaemia (CNL) is a rare myeloproliferative disease, mainly found in elderly patients
- This disease has a mostly fatal outcome—three quarters of our patients died within two years of diagnosis, mainly as a result of severe cerebral haemorrhage
- Two younger patients were successfully treated with allogeneic bone marrow transplantation or interferon, which resulted in haematological remission for years
- Thus, it is important to recognise CNL and to develop appropriate therapeutic strategies for affected patients.

**REFERENCES**

Chronic neutrophilic leukaemia: 14 new cases of an uncommon myeloproliferative disease

J Böhm and H E Schaefer

doi: 10.1136/jcp.55.11.862

Updated information and services can be found at:
http://jcp.bmj.com/content/55/11/862

**References**

This article cites 9 articles, 1 of which you can access for free at:
http://jcp.bmj.com/content/55/11/862#BIBL

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections

- Immunology (including allergy) (1664)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/