Myelodysplastic syndromes

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Myelodysplastic syndromes (MDS) include a heterogeneous group of clonal hematopoietic disorders, characterized by irreversible derangement in the development of the hematopoietic cell lines which result from the progressive impairment of precursor cell maturation and ineffective hematopoiesis (1, 2). MDS usually present with peripheral blood cytopenia of one or several cell lines and with a hyper- or normocellular bone marrow.

MDS most often occur as idiopathic diseases (primary MDS) in elderly people but may also occur after radiotherapy or chemotherapy (secondary MDS). Primary MDS have occasionally been described in children (3).

The current concept of MDS is that they represent the early phase of an acute, most often nonlymphoid leukemia (AML) or acute myelogenous leukemia (AML). An overt AL phase can supervene in one-third of the patients but this pathway of evolution is not obligatory and death is most commonly caused by infection or hemorrhage resulting from marrow failure.

Apoptosis plays a key role in MDS. It is related, in apparently opposite directions, to ineffective hematopoiesis and leukemic transformation; excessive apoptosis in the former and escape from apoptotic control in the latter. The cells undergoing apoptosis are restricted to 0D34 negative cells (maturing compartment) whereas 0D34-positive cells are almost never apoptotic (4-6). A possible unrestrained dual action of cytokines in the hematopoietic microenvironment is suspected. Candidates are tumor necrosis factor-a (TNF-a), transforming growth factor-ß (TGF-ß), interferon-y (IFN-y) and interleukin-1ß (IL-1ß) (5, 7). High proliferation activity of hematopoietic cells may be counteracted by the high level of medullary cell death, leukin-1ß (IL-1ß) (5, 7). High proliferation activity of hematopoietic cells and on lymphoid and myeloid progenitors. Its expression is normally confined to 0.1-0.5% of nucleated cells in marrow stem cells and on lymphoid and myeloid progenitors. Its expression is normally confined to 0.1-0.5% of nucleated cells in the peripheral blood and to 0.8-5% of mononuclear cells in adult bone marrow (25). An increased percentage of CD34-positive cells has been observed in bone marrow biopsy from MDS patients (25, 28). According to Oriani et al. (25), the presence of ALIP identifies patients with a worse prognosis, irrespective of the FAB subtypes.

0D34 immunostaining is a simple and reproducible investigation, which can be easily performed on routine bone marrow biopsies. P33 + MDS and AML correspond to a distinct group of marrow disorders characterized by a high rate of intramedullary cell death. The role of MDR multidrug resistance gene encoding for a transmembrane protein, P-glycoprotein (PGP)-expression is at the preliminary stage of understanding (11). It seems that PGP-expression is common in the cases of MDS with other poor prognosis factors. RAS genes have potent effects on the differentiation and proliferation program of cells and appear to be involved in primary and secondary myeloid leukemias. The RAS gene family has been associated with disease progression from MDS to AML (12).

The diagnosis of MDS relies on a combination of data, including clinical status, morphologic evaluation of the peripheral blood smear, bone marrow aspirate and biopsy specimen as well as cyto-genetic analysis.

The French-American-British (FAB) morphological classification (13) has allowed clearer delineation of MDS among workers as well as the publication of large series of patients. Five types of MDS are described according to the FAB proposals: refractory anemia, refractory anemia with ring sideroblasts, refractory anemia with excess of blasts, refractory anemia with excess of blasts in chronic myelomonocytic leukemia.

Scoring systems and multivariate analyses have generally demonstrated the prognostic value of age, the importance of cytopenias and the percentage of marrow blasts (14-17). An unfavorable cytogenetic group (patients with complex karyotypes) has been identified (18, 19).

Over the last 15 years, the introduction of bone marrow biopsies in MDS has led to consideration of histological prognostic parameters, such as cellularity, fibrosis, abnormal localization of immature precursors (ALIP) (20) and 0D34 immunohistochemistry. The use of the FAB classification on sections allows a better correlation between the cytology and biopsy specimens (21).

The negative prognostic impact of histological parameters, such as quantity of blasts, marrow fibrosis and ALIP has been demonstrated (14, 16, 20, 22-26). According to Oriani et al. (25), the presence of ALIP identifies patients with a worse prognosis, irrespective of the FAB subtypes.

The role of MDR multidrug resistance gene (MDR1) encoding a transmembrane protein, P-glycoprotein (PGP)-expression is at the preliminary stage of understanding (11). It seems that PGP-expression is common in the cases of MDS with other poor prognosis factors. RAS genes have potent effects on the differentiation and proliferation program of cells and appear to be involved in primary and secondary myeloid leukemias. The RAS gene family has been associated with disease progression from MDS to AML (12).
17.3% of 352 MDS patients presented with marrow fibrosis. Fibrotic cases were characterized by higher frequency of cytogenetic aberrations, lower value of hemoglobin and lower platelet counts, marrow hyperplasia, dysplasia in megakaryopoiesis and poor prognosis. A higher incidence of marrow fibrosis was observed in chronic myelomonocytic leukemia.

The differential diagnosis between fibrotic MDS and chronic myeloproliferative disease (idiopathic myelofibrosis, chronic myeloid leukemia) may be extremely difficult and borderline cases probably exist (29, 30). In this situation, clinical history, precise hematological data and chromosomal analysis are mandatory.

Although bone marrow is usually described as normo- or hypercellular in MDS, it appears to be hypoplastic in 7.7-19% of the cases, according to the literature (31, 32). Bone marrow cellularity does not appear to be an important factor in prognosis (33).

Differentiating hypoplastic MDS from aplastic anemia can at times be extremely difficult. Careful attention should be paid to the presence of clusters of blasts in the bone marrow biopsy. Significant morphological dysplasia (dysmegakaryopoiesis, presence of micromegakaryocytes and reticulin fibrosis) are essential in the diagnosis of MDS. The finding of a cytogenetic abnormality common to MOS and AML would support a diagnosis of MDS. Orazi et al. (32) have recently reported that immunohistochemistry could enable these conditions to be distinguished. They demonstrated that aplastic anemia is characterized by low expression of proliferating cell nuclear antigen in bone marrow and reduced CD34 frequency compared with MDS, supporting the concept of an early deficiency of stem cells in aplastic anemia.

Overlapping cases probably exist. Recently, increasing evidence has been collected supporting the hypothesis that acquired aplastic anemia, paracystic nocturnal hemoglobinuria and MDS may be linked by a common hematopoietic stem cell defect (34). Long-term observation of patients with acquired aplastic anemia demonstrates that the incidence of late clonal evolution after treatment with antilymphocyte globulin is much higher than previously suspected (35).

When considering the diagnosis of MDS on biopsy, the following entities must be considered in the list of differential diagnosis: i) marrow disturbances resulting from nutritional disorders (vitamin 12 or folate deficiencies), infectious diseases (tuberculosis, HIV and parvovirus infection) and toxic effects of drugs; ii) chronic myeloproliferative syndromes; iii) aplastic anemia; iv) paraplastic nocturnal hemoglobinuria; v) pure red cell aplasia; vi) hypoplastic leukemia; and vii) large granular lymphocyte disorders with cytopenia.

References
Pediatric preleukemic disorders

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For many pathologists, diagnosing preleukemic disorders is often a difficult diagnostic problem, not least because the incidence of these diseases is very low. Diagnosing preleukemic disorders in children is even more difficult. Bone marrow biopsies in these situations are usually seen only by pathologists in specialized centers. Nevertheless, every pathologist should know about preleukemic situations in childhood. The situation is not only complicated by the fact that most pathologists have little experience with pediatric bone marrow but also because there is little information about the normal histology of bone marrow in newborn and young children. Another complicating factor is the large spectrum of diseases that can develop into leukemia, many of which are very rare. A final complicating factor is that the diagnosis of these diseases is often based on very subtle and difficult to diagnose bone marrow changes.

Pediatric preleukemic disorders can be divided into three main groups: i) hereditary preleukemic disorders, clinically manifested by single-cell cytopenias as well as by pancytopenias; ii) primary myelodysplastic syndromes, including juvenile chronic myeloid leukemia and infantile monosomy-7; and iii) secondary myelodysplasia as a late complication of radiotherapy and/or chemotherapy.

Hereditary preleukemic disorders

Most syndromes involving bone marrow failure (single-cell cytopenias and pancytopenias of both the inherited and the acquired type) are, in at least a few patients, associated with the subsequent appearance of leukemia. These disorders involve the red cell series, the granulocytic series as well as lymphopoiesis abnormalities. In a number of cases all cell lines are involved. The most important single-cell cytopenias with an increased risk of development of leukemia are pure red cell aplasia, Kostmann’s syndrome and Shwachman’s syndrome. Pancytopenias with an increased risk of developing leukemia are Fanconi’s anemia, Bloom’s syndrome, aplastic anemia, and familial bone marrow failure. Other disorders with increased risk are trisomy-21 and ataxia telangiectasia.

Single cell cytopenias

Pure red cell aplasia

Pure red cell aplasia (Diamond-Blackfan anemia) is a severe macrocytic or normocytic anemia characterized by an isolated depletion of erythroid precursors. The disease is usually seen in the first year of life.

The pathogenesis of the disease is probably an intrinsic defect of the erythroid precursor cells. Histologically, most bone marrow shows erythroid hypoplasia or aplasia. Many congenital abnormalities are seen in children with pure red cell aplasia among which abnormalities of the head and upper limbs are prevalent. There is a slightly increased risk of acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS).

Kostmann’s syndrome

Kostmann’s syndrome is a rare disease, also known as infantile genetic agranulocytosis. It is also referred to as severe chronic neutropenia. Usually, children with this disease develop severe pyogenic infections and extreme neutropenia in the first half-year of life. Histologically, the bone marrow shows an absence or markedly decreased number of myeloid precursors. Most patients die of infections and some develop AML.

Schwachman’s syndrome

Schwachman’s syndrome is a rare multiorgan disorder characterized by a variable neutropenia in patients with a large number of other abnormalities. Disease symptoms may resemble those of cystic fibrosis. Approximately 25% of the patients develop aplastic anemia. The bone marrow is histologically usually hypocellular. Occasionally MDS or AML is seen.

Pancytopenias

Fanconi’s anemia

Fanconi’s anemia is the most common inherited form of congenital pancytopenia. It may take years before the hematological abnormalities reveal themselves. Bone marrow examination shows hypoplastic or aplastic bone marrows, often with dyserythropoiesis. Bloom’s syndrome and ataxia telangiectasia are characterized by pancytopenic marrow failure.

Primary myelodysplastic syndromes

Primary myelodysplastic syndromes are characterized by maturational disturbances resulting in ineffective hematopoiesis, morphological abnormalities in one or more cell lines and an increased chance of developing acute leukemia. The different MDS subgroups of the French-American-British (FAB) classification apply also to children.

In addition, juvenile chronic myeloid leukemia and the infantile monosomy-7 syndrome are incorporated in the pediatric MDS group.

Juvenile chronic myeloid leukemia

Juvenile chronic myeloid leukemia is a chronic myeloid leukemia without the Philadelphia chromosome. It is characterized by a marked monocytosis and high fetal hemoglobin levels. The peripheral blood and the bone marrow cells show dysplastic features and the prognosis of this disease is poor.

Infantile monosomy-7

The prominent feature of this disease is monosomy or partial deletion of chromosome-7. The histology of this disease is the same as that of the other myelodysplastic diseases. Since monosomy-7 is also seen in other myelodysplastic and leukemic disorders, infantile monosomy-7-related MDS is only diagnosed in children under 3 years of age. The prognosis is relatively good with 40% of the patients surviving 5 years.
Secondary myelodysplastic syndrome
Secondary myelodysplastic syndrome is seen as a complication of radiotherapy and/or chemotherapy. Several papers have reported the development of MDS post-therapy in children. Juvenile chronic myeloid leukemia and infantile monosomy-7 do not occur as secondary myelodysplastic disorders.

References

Bone marrow involvement in non-Hodgkin’s lymphoma according to the REAL classification
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Introduction
The Revised American European Lymphoma (REAL) classification, a proposal by the International Lymphoma Study Group, was published in 1994. This classification was an attempt to simplify the existing plethora of lymphoma classifications, to update them with recent phenotypical and genotypical data and, most importantly, to offer a reproducible classification acceptable to both Europeans and Americans. While the Working Formulation published in 1982 was indeed meant to serve as a translation system between the various classifications, it became very popular in the United States as “a classification on its own”; in contrast, European pathologists continued to use the Kiel classification. Moreover, it should be noted that both classification systems were based on pure morphology as cases were studied on hematoxylin and eosin or Giemsa stained sections only. To complicate the situation even more, lymphomas presenting with blood and/or bone marrow involvement were identified as lymphoid leukemias but were separately subtyped according another classification, which was proposed by the French American British (FAB) group. As immunohistochemistry and flow cytometry for phenotyping lymphomas became widely performed and as genotyping on these neoplasms became possible, these lymphoid malignancies were better understood and “new” lymphoma-entities were identified. As the lymphoma classifications used until then needed to be revised, a new proposal was necessary. Bone marrow examination is a routine procedure in the staging post-therapy follow-up of patients with non-Hodgkin’s lymphoma. In addition, this investigation may serve as “the” diagnostic tool in certain subtypes of lymphoma and in clinical settings in which enlarged peripheral nodes are absent or splenomegaly is the sole presenting finding. Bone marrow investigation should include trephine biopsy sections (and trephine imprints) as well as aspirate smears and may be completed by the examination of blood smears. All these specimens contribute to the final diagnosis and frequently complement one another.

Traditionally, the morphological evaluation of a bilateral trephine biopsy is the method of choice in assessing bone marrow involvement in lymphoma. In view of the REAL classification, the use of previously defined criteria, such as the number and growth pattern of the lymphoid infiltrates and/or the cytological features of the lymphoid cells in the trephine, is not always helpful in identifying the biological meaning of these infiltrates or in subtyping the lymphoma.

Identification of the biological meaning of lymphoid infiltrates in the trephine
The usefulness of phenotyping on paraffin-embedded trephine sections is limited; frozen sections theoretically allow for a more extended panel of antibodies to be applied but this technique is more demanding and difficult to incorporate in a routine practice. Moreover, incorrect interpretation of the staining results may occur. Alternatively, immunophenotyping may be performed on bone marrow aspirate samples but may give discordant results due to sample variation between the trephine biopsy and the bone marrow aspirate.

With the development of molecular biological techniques such as the polymerase chain reaction (PCR), it has become possible to recognize the clonal character of lymphoid infiltrates by analyzing the presence of lymphoma-specific genetic translocations or clone-specific antigen receptor gene rearrangements. In addition, due to its increased sensitivity, the PCR technique offers the potential to detect small numbers of malignant cells, allowing the monitoring of minimal residual disease.

Detection of minimal residual disease is mostly performed in peripheral blood and bone marrow aspirate samples because these samples can be freshly processed. Bone marrow trephine biopsies, which have been fixed and decalcified, are more problematic but they may be analyzed with some PCR techniques. However, in our experience as well as in that of others, the analysis on bone marrow sections of light gene rearrangements with the PCR technique works well and this technique may be more sensitive than morphological and immunohistochemical analysis.

Subtyping non-Hodgkin’s lymphomas
Whether a correct subtyping of the lymphoma is possible using the previously described growth pattern and/or the cytological features of the trephine infiltrate is debatable. A reevaluation of these morphological parameters, based on a detailed analysis of fully documented cases and taking the REAL classification into account, seems to be mandatory. At present we have such a study underway, including more than 300 cases documented by phenotypical and genotypical data. Our first results indicate that in comparison with blood smears and bone marrow smears, the study of bone marrow trephines offers the most sensitive technique for detecting lymphomatous infiltrates. Nevertheless, preliminary results indicate that the various growth patterns as defined in the past (nodular, interstitial, massive and paratrabecular) are not specific to all lymphoma subtypes and that cytological features of the lymphomatous infiltrate may be misleading. While this phenomenon has been described for nodal large cell lymphomas, as they may present with a small cell component in the trephine, it is less well known that the cytological features of the lymphomatous infiltrate in the trephine does not always allow the various subtypes of small cell lymphomas to be cor-
rectly differentiated. Finally, our preliminary results also point towards trephine as the most informative and occasionally unique material for identifying certain particular lymphoma entities.

Conclusion

Histological examination of the bone marrow based on an evaluation of trephine biopsies is the gold standard for the diagnosis of bone marrow involvement in non-Hodgkin's lymphomas while immunohistochemistry and molecular analysis may increase the accuracy and the sensitivity of lymphoma detection. Subtyping lymphomas on the trephine, according to the REAL classification, needs further investigation.

References


Table 1. Morphometric characteristics (mean ±SD) at diagnosis of patients regarding several bone marrow features in Ph1- chronic myeloproliferative disorders compared with a control group.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Normal bone marrow</th>
<th>Polycythemia vera</th>
<th>Idiopathic myelofibrosis</th>
<th>Essential thrombocythemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellularity (%)</td>
<td>50.5±13.9</td>
<td>88.1±7.9</td>
<td>81.9±12.4</td>
<td>70.8±6.6</td>
</tr>
<tr>
<td>Erythropoiesis x10^4/mm^3 (Ret 40%)</td>
<td>14.6±2.7</td>
<td>36.9±6.7</td>
<td>7.2±3.8</td>
<td>16.1±3.0</td>
</tr>
<tr>
<td>Granulopoiesis x10^3/mm^2</td>
<td>39.0±6.3</td>
<td>58.7±8.8</td>
<td>40.1±25.0</td>
<td>37.4±6.3</td>
</tr>
<tr>
<td>Megakaryopoiesis x10^1/mm^2 (naphthol-AS-D-chloroacetate esterase reaction)</td>
<td>24.4±5.3</td>
<td>102.6±24.2</td>
<td>79.9±29.9</td>
<td>126.6±35.6</td>
</tr>
<tr>
<td>Macrophages x10^2/mm^2 (20068)</td>
<td>3.0±1.2</td>
<td>3.9±1.2</td>
<td>7.4±1.3</td>
<td>3.7±0.7</td>
</tr>
<tr>
<td>Fibers x10^2/mm^2 (Gomori's stain)</td>
<td>16.1±5.1</td>
<td>21.6±10.3</td>
<td>93.5±32.8</td>
<td>14.9±6.1</td>
</tr>
<tr>
<td>Fraction with myelofibrosis (%)</td>
<td>0</td>
<td>17</td>
<td>84</td>
<td>0</td>
</tr>
</tbody>
</table>

Because of the wide ranges, corresponding values (in brackets) are given for megakaryocytes and fibers. The incidence of (reticulin + collagen) myelofibrosis for all entities (cut-off point, doubling of normal reticulin stain, measured fiber density) is also indicated.

Philadelphia chromosome-negative (Ph1-) chronic myeloproliferative disorders. A synoptic approach

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Progress in the understanding and definition of the three main subtypes of Ph1- chronic myeloproliferative disorders (CMPDs), idiopathic (primary) myelofibrosis (IMF), polycythemia vera (PV) and essential thrombocythemia (ET) seems to be most promising when pursuing a synoptic approach to this problem. This implies not only close cooperation with the clinicians and reference to hematologi-
improve the impact of risk profiles (Table 3). Thus a substantial advance in diagnostic and prognostic efficiency may be achieved by a concerted action involving a refined histological evaluation.

Table 2. The Cologne Criteria (4) for the diagnosis and staging of idiopathic myelofibrosis (IMF).

<table>
<thead>
<tr>
<th>Diagnosis and classification of IMF is acceptable if the following combinations are present:</th>
</tr>
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<tbody>
<tr>
<td>Stage 1: A+B+C+F1 is consistent with a hypercellular (prefibrotic) stage simulating clinically essential thrombocythemia</td>
</tr>
<tr>
<td>Stage 2: A+B+C+D+F2 is consistent with early IMF</td>
</tr>
<tr>
<td>Stage 3: A+B+D+F3 is consistent with manifest IMF</td>
</tr>
<tr>
<td>Stage 4: A+B+D+E+F3+4 is consistent with advanced IMF complicated by osteosclerosis (osteomyelosclerosis)</td>
</tr>
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</table>

Table 3. Simplified synthesis prognostic staging system (Cologne score) in idiopathic (primary) myelofibrosis (IMF) derived from a clinicopathological study on 120 patients (13).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prognostic impact (score)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>&gt;70 2</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>&lt;10 2</td>
</tr>
<tr>
<td>Thrombocytes (x 10^9/l)</td>
<td>&lt;300 1</td>
</tr>
<tr>
<td>Leukocytes (x 10^6/l)</td>
<td>&gt;20 1</td>
</tr>
<tr>
<td>Myeloblasts (%)</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Erythroblasts (%)</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Proliferating cell nuclear antigen index (per mm3)</td>
<td>&lt;240 0.5</td>
</tr>
<tr>
<td>Apoptosis (per mm3)</td>
<td>&lt;6 0.5</td>
</tr>
</tbody>
</table>

Diagnosis and classification of IMF is acceptable if the following combinations are present:

| Stage 1: A+B+C+F1 is consistent with a hypercellular (prefibrotic) stage simulating clinically essential thrombocythemia |
| Stage 2: A+B+C+D+F2 is consistent with early IMF |
| Stage 3: A+B+D+F3 is consistent with manifest IMF |
| Stage 4: A+B+D+E+F3+4 is consistent with advanced IMF complicated by osteosclerosis (osteomyelosclerosis) |

**Chronic myelogenous leukemia. An update**

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Chronic myelogenous leukemia (CML) comprises four groups that are under discussion at present. These are: i) Philadelphia (Ph)-positive, BCR-positive CML; ii) Ph-negative, BOR-positive CML; iii) atypical CML (aCML), i.e. Ph-negative, BOR-negative aCML; and iv) chronic myelomonocytic leukemia (CMML), which actually belongs into the myelodysplastic syndromes but which must be discussed in this context. The first group is by far the largest, with over 90% occurrence among all CMLs. The second group is believed to form about 4% (1). CMML is presumed to have approximately 3% frequency and the new category of aCML is even more rarely observed (2-4). Neutrophil leukemias are seldom detected and are thus not considered within this article. Recent results of bone marrow pathology focus on the large group of Ph-positive CML and on Ph-negative, BCR-positive CML since patients of the second group have similar clinicopathological characteristics and outcome (1, 2, 5). Patients of both groups benefit from protocol therapy with interferon-alpha-2 (IFN-alpha) or hydroxyurea, which has prolonged their mean life expectancy from 3-4 years to about 5 years overall survival (5, 6).

**References**

The role of histopathology from bone marrow biopsies is still widely underestimated because the results from relevant therapy trials are presented without regard for protocol biopsies (7), as previously performed by Rozman’s group in Spain (8). Meanwhile, histopathology has provided data on morphological criteria, which characterize the progression of Ph-positive CML. Such criteria are number and cytomorphology of megakaryocytes, grade or number of fibers and percentage of blasts in bone marrow sections (10,11). By grading or quantifying these three criteria, the comparison of diagnostic with sequential biopsy measuring has provided new insights into bone marrow fiber increase under myelosuppressive therapy with busulfan or IFN (9,10). A strict grading and staging of these morphological criteria proves that the initial density of fibers or blasts in chronic myeloproliferative disorder (CMPD) patients represents a reliable prognostic indicator of progressing myelofibrosis or blast crisis, at least in randomly collected patients (9,10).

Density of megakaryocytes is closely related to the onset and progress of fibrosis in bone marrow as proven by different laboratories (9-12). Preliminary evaluation of this topic from the bone marrow biopsies of some 300 patients from the German CML trial I (5, 6), provide a significant correlation between the grade of megakaryocytic density and progress into myelofibrosis during a 3-year mean observation (9).

Immunohistochemical analysis of morphological criteria was provided especially by Thiele’s group, who studied the effect of IFN on megakaryocytes by evaluating patients from monocenter trials (11,12). The probability of unmasking the prognostic impact of a histological criterion by morphological investigation increases significantly when large numbers of well-documented patients can be evaluated. Thus, multicenter sampling of bone marrow probes from different hospitals must be pursued over a long period of time. Such methodology and rationale, however, by necessity provide a different handling of bone marrow tissue by varying handling, mainly by fixation procedures, bone marrow concentrations as well as the times of exposure. These varying technical procedures must inevitably influence the susceptibility of the epitopes of investigated cells to the immunoreactions.

The impact of pseudo-Gaucher-cells (PGC) on the prognosis of Ph-positive CML is not totally clear at present (3, 9). These birefringent storing histiocytes can be detected in almost 70% of diagnostic bone marrow biopsies (13) and are rarely revealed in Ph-negative, large megakaryocytic chronic myeloproliferation. However, PGC do also occur in aCML. Positive prognostic influence in PGC-positive patients is reported in overall survivals (10,12). This can be reconfirmed by a recent biomathematical update among the 308 patients of the German CML trial I, while all previous statistical analyses had failed (unpublished data). However, a semiquantitative distinction between patients with numerous PGC versus those with few or no PGC in their diagnostic bone marrow biopsy discloses a completely different result: patients with numerous PGC have a significantly worse overall survival than those with few PGC (unpublished data). The question at present is whether the occurrence of PGC is correlated with other histological features of prognostic relevance.

aCML is hematologically similar to CML (1-4), being negative for Ph-translocation and for BCR-ABL transcripts in reverse transcription-polymerase chain reaction (RT-PCR) analysis (14,15). Its distinction from CMML either by quantitative cytology of peripheral blood and bone marrow was described by the French-American-British (FAB) group (4). Although some could reconfirm this cytological distinction between aCML and CMML by simple criteria of the differential count of peripheral blood and the absence of dysplasia among the myelopoiesis of the bone marrow (16), others are discussing whether CMML may be generally grouped within CMPD (17), or whether it should remain within the MDS (18). This difference of opinion is not based upon the histopathology of bone marrow biopsies and few data were presented on the histological definition of the new entity of a CML (2-4). Histological diagnosis of an aCML is based in our laboratories on a marked increase of granulopoiesis which shows dysplasias of its cells, megakaryocytes which are not as small as in Ph+ CML, and very few (3) basophils within the bone marrow and peripheral blood. Hehlmann et al. observed that these patients with aCML are older than those with Ph-positive CML, have lower cell counts and are more ill at diagnosis. Their median survival is 1.4 vs. 4.2 years in Ph-positive CML (5-7).

In conclusion, a detailed morphological analysis of diagnostic and sequential bone marrow biopsies, i.e., staging by at least semiquantitative histology, is recommended if the long-term effects and interrelations with myelosuppressive treatment are to be revealed. Additionally, histopathology must respect the differential diagnosis among the CML-groups and aCML must be defined histologically by investigating patients that are well characterized by clinical and genetic analysis.

References