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Editorial

Prognostic implications of bone marrow features in chronic myelogenous leukaemia

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In the past two decades research in haematology has been focused predominantly on the malignant lymphomas, acute leukaemias, including their precursor lesions (myelodysplastic syndromes) and various aspects of molecular biology. However, as a consequence of greatly increased use of the bone marrow trephine biopsy technique as well as the introduction of new therapeutic regimes, interest in the clinical and morphological features of chronic myeloproliferative disorders (CMPDs) has been re-awakened in recent years. Among the different subtypes of CMPDs chronic myelogenous leukaemia (CML) is not only the most frequent entity (about 60%), but also characterized by poor survival under conventional chemotherapy and interferon therapy (Kantarjian et al. 1988; Sokal et al. 1988a, b; Hehlmann et al. 1992; Morra et al. 1992). For this reason, it is understandable that several authors have tried to determine factors which may aid in assigning patients to different prognostic subgroups (Kantarjian et al. 1990) or could influence the exact timing of marrow transplantation as the only curative treatment (Segel et al. 1986; Kantarjian et al. 1988).

Generally, any attempt to define disease features of predictive value has to take into account several points. First, variables which were assumed to exert a prognostic impact should be divided into static and dynamic ones. Static variables are those present on admission or at the time of diagnosis and may reflect the stage to which the disease has progressed. Dynamic determinants of survival are mostly compatible with therapy-associated patterns of response and evolution of clinical findings during the course of disease and may indicate aggressiveness. Second, statistical evaluation has to involve multivariate regression methods to exclude the impact of the multiple interactions among the different disease features and to identify those variables with primary prognostic significance. Using proportional hazards models enables the computation of the relative prognostic values associated with prognosis for any patient. Following this calculation patients can be categorized into high, intermediate and low risk groups with median survivals of approximately 2, 3 and 4.5 years (Kantarjian et al. 1988; Sokal et al. 1988a, b). Third, in order to eliminate the effect of mortality from other causes of death, relative survival rates and life expectancies have to be assessed. This method is best employed in elderly patients, in whom interactions between CML and various fatal aging process-related disorders may be expected (Thiele et al. 1991). In this context it should be kept in mind that only in a minority of CML patients are autopsy findings available to establish the exact cause of death.

In only a few larger series which include data from national and international CML trials has multivariate regression analysis of the various associations of patient characteristics and therapy with survival been performed (Cervantes and Rozman 1982; Sokal et al. 1984; Kantarjian et al. 1985; The Italian Cooperative Study Group 1991; Hehlmann et al. 1992). In the most widely accepted risk model (Sokal et al. 1984), which is particularly applied to evaluate prognosis and timing of bone marrow transplantation (Kantarjian et al. 1985; Sokal et al. 1988a; The Italian Cooperative Study Group 1991), static factors of prognostic importance comprised age, platelet count, spleen size and peripheral blasts (Sokal et al. 1984). Other staging systems which have been described in detail in the literature include race, liver size, white blood cell count, basophils, promyelocytes, nucleated red cells in the peripheral blood (Kantarjian et al. 1990), and chromosomal aberrations other than the well-known Philadelphia translocation (t9;22) and so-called Philadelphia-chromosome-negative patients (Kantarjian et al. 1985; Sokal et al. 1988b). Dynamic factors of prognostic significance such as evolution of accelerated disease features and response to therapy (Kantarjian et al. 1988) were rarely addressed. However, in all these previous multivariate analysis-derived risk scores there was no calculation of the relative survival rates and, most remarkably, no histological parameters were considered. This striking lack of information regarding bone marrow lesions of predictive value may be due to the

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fact that a trephine biopsy was apparently not a criterion for entry of a patient into one of the major clinical trials on CML (Sokal et al. 1984; Kantarjian et al. 1985; The Italian Cooperative Study Group 1991). Morphological diagnosis of CML was usually limited to peripheral blood findings and aspirate cytology; using this latter method does not permit us to determine quantitative aspects of the cellular elements composing haematopoiesis, or to evaluate the content of fibres.

The extensive application of bone marrow biopsies in CML has demonstrated convincingly that in a significant number of patients the characteristic granulocytopoietic myeloproliferation with reduction of the erythroid cell lineage may be accompanied by other features. These features consist of an increased growth of (micro-) megakaryocytes, occurrence of reticulin and collagen fibres and, finally, numerous macrophages, that is to say histiocytic-phagocytic reticular cells (Lazzarino et al. 1986; Burkhardt et al. 1990; Georgii et al. 1990; Thiele et al. 1991; Buhr et al. 1992). This conspicuous variability in the appearance of the bone marrow in CML has served as a basis for histological classification systems which aim to discriminate subgroups of patients with differences in clinical findings and survival (Burkhardt et al. 1990; Georgii et al. 1990). Briefly, subgroups with a predominantly granulocytic proliferation were regarded as common type of CML and separated from those showing an increase in megakaryocytes. Further distinctions between advanced stages of the disease process and subgroups revealing myelofibrosis and blastic transformation were made. This so-called Hannover Classification (Georgii et al. 1990) has to be recognized as a first attempt to evaluate the histological parameters of presumptive impact on prognosis in CML. Another approach to this problems is an univariate analysis-derived computation of certain histomorphological variables (such as fibres) by semiquantitative scoring systems (Lazzarino et al. 1986; Dekmezian et al. 1987) or a morphometric evaluation of the different marrow elements (Thiele et al. 1990). In consideration of the heterogeneity of the different CML populations investigated by a wide spectrum of statistical methods and the controversial issue as to whether histological factors may predict survival, four variables were selected which are currently under discussion to exert prognostic significance.

Fibres

Different degrees of reticulin and/or collagen fibre deposition within the bone marrow may be found on admission of CML patients, in about 25% of cases (range 10–47%), depending on the various definitions of myelofibrosis (Gralnick et al. 1971; Lazzarino et al. 1986; Dekmezian et al. 1987; Anger et al. 1990; Georgii et al. 1990; Thiele et al. 1991). It is generally agreed that myelofibrosis represents an advanced stage of the disease process and may be an immediate precursor of blastic crisis (Gralnick et al. 1971; Kantarjian et al. 1988). Development of fibrosis reveals a significant correlation with the duration of relevant prediagnostic symptoms and consequently its negative influence on survival is due to later diagnosis of CML (Thiele et al. 1986). In several studies performed to evaluate the predictive impact of this parameter, a worsening of life expectancy has been found in patients with a significant content of reticulin or collagen fibres (Lazzarino et al. 1986; Dekmezian et al. 1987; Kantarjian et al. 1988; Anger et al. 1990). Quantitation of fibre accumulation was, however, restricted to semiquantitative gradings using different scores. Morphometry with determination of argyprophilic fibre density has disclosed that only a slight increase in reticulin, just exceeding the upper limit of the normal value, was correlated with an unfavourable prognosis. Moreover, as was expected, multiple interactions existed between clinical and other histological variables (Thiele et al. 1990). For this reason, it is understandable that those categories of the so-called Hannover Classification (Georgii et al. 1990) which comprise reticulin or collagen fibrosis are thought to be associated with a significant shortening of life expectancy.

Megakaryocytes

Evaluation of megakaryocytes as suspected factors of prognostic significance is a controversial issue which is additionally complicated by a striking relationship with the evolution of myelofibrosis (Lazzarino et al. 1986; Georgii et al. 1990; Thiele et al. 1990; Buhr et al. 1992). As already mentioned, the frequent occurrence of megakaryocyte proliferation simultaneously with reticulin or collagen fibrosis is associated with an unfavourable prognosis (Lazzarino et al. 1986; Dekmezian et al. 1987; Kantarjian et al. 1988; Anger et al. 1990; Thiele et al. 1990, 1991). When compared with a prevalent granulocytic proliferation, the most frequent and common subtype of CML (Georgii et al. 1990), an isolated increase in megakaryocyte numbers without myelofibrosis has not to be considered as exerting an adverse influence on survival. It may be assumed that cases with an increased megakaryocyte growth alone reflect a relatively early "pre-myelofibrotic" stage of disease (Buhr et al. 1992), which explains its favourable prognostic impact. As a discordant finding megakaryocytopenia was recorded by one study group to indicate poor survival (Kantarjian et al. 1985, 1988). In this context it is noteworthy that the marrow samples of the latter authors involved some aspirates, and an unknown number of patients were referred within 3 months of diagnosis and after minimal therapy. Furthermore, by applying conventional staining methods (haematoxylin and eosin, Giemsa, periodic acid-Schiff) only mature, well-differentiated megakaryocytes are identifiable. However, following immunohistochemistry with monoclonal antibodies against platelet glycoprotein IIIa (CD61) or the alpha-naphthyl acetate esterase reaction, atypical micromegakaryocytes and precursor forms (pro- and megakaryoblasts) become recognizable. Presently, it cannot be excluded that this abnormal and immature cell population might exert a predictive value. This point needs further clarification, particularly because atypical micromega-

karyocytes are a conspicuous feature in CML (Burkhardt et al. 1990; Georgii et al. 1990; Thiele et al. 1990; Buhr et al. 1992).

Blasts

Appearance of a significant myeloblastic cell population in bone marrow biopsies of patients with CML is a hallmark of an impending transformation into an accelerated or unstable phase. Myeloblasts as histological parameters have only a bearing on survival in those series of patients in which a relatively high peripheral blast count (more than 20%) was not excluded explicitly.

Pseudo-Gaucher cells

Although bone marrow in CML harbours numerous macrophages, only the subgroup of pseudo-Gaucher cells, sea-blue histiocytes and intermediate cell elements display a remarkably specific and most favourable impact on prognosis. This finding has been reported in smaller series of patients (Albrecht 1972; Thiele et al. 1986; Kelsey and Geary 1988) and, like fibrosis, retains its predictive value even in multivariate analysis (Thiele et al. 1991). The occurrence of pseudo-Gaucher cells has generally been linked with an increased turnover of granulo- and erythrocytes (Kelsey and Geary 1988). It is suggested that abnormal storage of glycolipids and transformation of macrophages into this peculiar cell population is prevalent in those CML cases where an imbalance develops between leucocyte death and degradation capability of the mononuclear-phagocyte system. Following this hypothesis pseudo-Gaucher-cell-positive cases indicate an enforced auto-aggressive activity to reduce the leucocyte mass, which may explain their favourable prognosis.

Because of the retrospective and exploratory character of the determination of prognostic variables, validation of predictive capacities should include larger and more homogeneously distributed series of patients than has been investigated to date. Further, a complete assessment of the corresponding histological features with employment of (immuno-) histochemistry and suitable statistical methods are required. Future analysis with an independent set of data which have been collected in the course of on-going clinical trials on CML is essential to emphasize the prognostic significance of bone marrow findings in addition to clinical-laboratory findings. In this context endeavours should be aimed at an amendment of the currently applied risk models (Kantarjian et al. 1990) by inclusion of certain histological variables, among which fibres and pseudo-Gaucher cells are considered to have a specific prognostic impact.

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