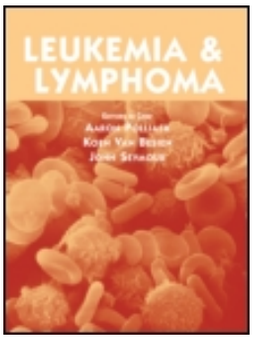

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COMMENTARY

Bone marrow fibrosis: a prognostic scar in hematological malignancies

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Idiopathic myelofibrosis (IMF) is a chronic clonal myeloproliferative disorder of bone marrow (BM) hematopoietic stem cells, characterized by the proliferation of cells mostly of the megakaryocytic and granulocytic lineages and accompanied by reactive deposition of reticulin fibers [1]. Myelofibrosis develops sequentially from an initial prefibrotic hypercellular phase with minimal deposition of reticulin, to a more obvious phase of marrow fibrosis associated with extramedullary hematopoiesis in the spleen, liver and other sites [2]. These findings in the bone marrow are accompanied by characteristic peripheral blood morphology with a leukoerythroblastic picture and progressive splenomegaly and hepatomegaly, and are associated with other clinical manifestations, most commonly anemia, leukocytosis or leukopenia, thrombocytosis and constitutional symptoms [1]. In recent years, various scoring systems have been suggested to grade the amount of reticulin and collagen fibers in the BM, and the most widely accepted model is the four-grade scoring system recommended by the European consensus [3]. Generally the extent of fibrosis appears to correlate not only with lower hemoglobin levels, the appearance of a higher percentage of blasts in the peripheral blood and larger spleens, but also with the recognized International Prognostic Scoring System (IPSS) risk assessment parameters.

In this issue of ***Leukemia and Lymphoma***, Nazha and colleagues report the prognostic implications and clinical characteristics associated with BM fibrosis in a large retrospective series of patients with IMF [4]. Despite the fact that various studies suggest that BM fibrosis (BMF) may affect overall survival (OS) in patients with IMF [5–7], this issue still remains controversial, as seen from the results described here by Nazha *et al*. [4]. They report similar rates for OS, event-free survival (EFS) and transformation to acute leukemia among patients with different grades of BMF. However, higher grades of fibrosis were seen to be associated with a lower level of hemoglobin, white blood cells and platelet counts, higher percentages of blasts in the peripheral blood, and significantly larger spleen and liver size. In addition, survival risk assessment of patients using the different international scoring systems also correlated with the severity of BMF in these cases.

Other studies have also reported the prognostic significance of grading BMF in IMF, and patients with more severe fibrosis had inferior OS compared to those cases with minimal fibrosis [5–7]. Earlier in 2006, Thiele and Kvasnicka [7] had already reported inferior OS among patients with higher grades of BMF, but statistical significance was not documented.

Since the natural history of other myeloproliferative neoplasms (MPNs) is also characterized by progression of BMF, some investigators evaluated the clinical significance of fibrosis in MPNs such as chronic myeloid leukemia [8] and polycythemia vera [9], and demonstrated that patients with abnormal fibrosis have poorer responses to imatinib [8], and seem to be less prone to develop thrombotic phenomena [9]. Increased reticulin fibrosis has also been described in BM malignancies other than MPNs, including myelodysplastic syndromes [10] and acute lymphoblastic leukemia [11]. Very recently we also described the incidence and prognostic significance of BMF in "treatment naive" patients with chronic lymphocytic leukemia (CLL) [12], and identified a significant correlation between poor OS and more advanced grades of BM reticulin fibrosis. Furthermore, it is worthwhile to recall that BMF is not only restricted to malignancy, but can also be encountered in other disorders such as chronic immune thrombocytopenic purpura, where its occurrence is associated with clinical features including age, sex and baseline platelet count [13]. Taking all the above data into consideration, one may conclude that the extent of BMF not only influences the clinical course of MPNs but may also play an important role in the outcome of other hematological disorders involving the bone marrow.

Until quite recently the pathogenesis of BMF has been poorly understood, but in the past few years some novel molecular pathways have been described that may be linked to this phenomenon, the most relevant being the JAK-STAT (Janus kinase–signal transducer and activator of transcription) signaling pathway. The discovery of the JAK2 V617F somatic mutation led rapidly to the development of

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a novel class of drugs, the JAK inhibitors. The use of these novel JAK2 and JAK1 inhibitors in patients with MPNs has had some impact on disease burden, and a decrease in bone marrow fibrosis has also been recorded in some cases [14]. Several new compounds with other mechanisms of action are now available, including monoclonal antibodies targeting transforming growth factor-β and the lysyl oxidase gene family, and these may also prove to be effective in the reversal of bone marrow fibrosis in the near future [15,16]. In very recent work, our group has shown that several members of the lysyl oxidase gene family, known to be involved in the generation of reticulin fibers, are overexpressed in MPNs, and in particular in idiopathic myelofibrosis [16]. These agents, which interfere with novel pathways involved in the pathogenesis of reticulin and collagen fibrosis, are currently being investigated as single agents or in combination with JAK2 inhibitors for therapy of myelofibrosis [15].

Therapeutic advances in bone marrow transplant may also be important in this regard, and recently Kröger *et al*. described rapid total regression of advanced bone marrow fibrosis after reduced intensity allogeneic transplant [17]. Taken together, these results imply that fibrogenesis in the BM is a dynamic process, not a static event, and may still be reversible even in an advanced stage [17]. Additional clinical and biological studies and longer follow-up periods are still needed to fully understand the significance and impact of BMF in MPNs. Although it is clearly evident that the grade of fibrosis affects the clinical course in a variety of hematological malignancies including IMF, it is of some comfort to realize that regression may occur using the newer agents and procedures developed. These are already knocking on the door and awaiting entry for patients with myelofibrosis.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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