more frequently in association with doxorubicin-containing regimens.\textsuperscript{7} We report here on an unexpectedly high incidence of DVT in patients with newly diagnosed, symptomatic MM who received first-line therapy with thalidomide-dexamethasone. By study design, both drugs were administered for 4 months in an attempt to reduce tumor cell mass before collection of peripheral blood stem cells to support 2 subsequent autotransplants. The starting dose of thalidomide was 100 mg/d, with a subsequent increase to 200 mg/d after 14 days; the monthly dose of dexamethasone was 40 mg/d for 4 days, with cycles repeated on days 9 to 12 and 17 to 20 on the first and the third month of therapy. At the present time, 19 patients entered this phase II trial and received at least 2 months of therapy. Of these 19 patients, 5 (26\%) had symptomatic DVT, of whom 1 had associated nonfatal pulmonary embolism. DVT was documented by doppler ultrasonography and developed in the lower extremities (popliteal vein: 3 patients; calf veins: 2 patients). Thrombosis occurred during the first month of therapy in 2 patients, the second month in 1 patient, the third month in 1 patient, and at the end of the fourth month of therapy in the last patient. Baseline laboratory evaluation for inherited risk factors for thrombosis—including antithrombin III deficiency, protein C and protein S deficiencies, resistance to activated protein C, lupus anticoagulant and antiphospholipid antibodies, and prothrombin gene abnormalities (G20210A)—was performed in all patients and excluded primary hypercoagulable states. Additional risk factors for thrombosis included hormonal therapy in a single patient. Anticoagulation therapy consisting of low-molecular-weight heparin with or without warfarin was promptly started after the diagnosis of DVT. There were 3 patients who safely continued thalidomide-dexamethasone without evidence of progression of DVT; thalidomide was stopped in the other patients, 1 with associated pulmonary embolism and 1 by study design before priming therapy with high-dose cyclophosphamide. In addition to recent reports on the use of thalidomide administered in combination with multiagent chemotherapy and dexamethasone,\textsuperscript{4,5} present data show an increased risk of DVT also for patients with MM receiving first-line thalidomide-dexamethasone. This observation was not reported in previous studies with the same regimen, but different thalidomide and dexamethasone dose intensities, as salvage therapy for patients with advanced and refractory MM.\textsuperscript{7,8} Efforts aimed at elucidating biologic mechanisms associated with thrombosis and thalidomide-based therapy should continue. In the interim, careful monitoring for DVT should be recommended for patients enrolled in investigational clinical trials including thalidomide as part of therapy for MM. In these patients prophylactic low-dose warfarin should be considered in an attempt to reduce the risk for DVT.

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References


To the editor:

Involvement of the \textit{MLL} gene in T-lineage acute lymphoblastic leukemia

Translocations involving 11q23 are considered synonymous with rearrangements of the \textit{MLL} gene. They are usually associated with B-lineage acute lymphoblastic leukemia (ALL) and acute myeloid leukemia but have also been reported in T-lineage ALL.\textsuperscript{1-6} Although most can be identified by routine cytogenetic analysis, their prognostic importance means that molecular methods are frequently employed to ensure detection.

Recently, Hayette et al\textsuperscript{7} reported the results of screening 81 patients with T-ALL for the involvement of the \textit{MLL} gene using Southern blotting, reverse transcriptase–polymerase chain reaction (RT-PCR), and fluorescence in situ hybridization (FISH). They reported that 4 of 47 (8\%) adults and 0 of 34 children had a rearrangement of the \textit{MLL} gene. Using molecular methods, 3 cases with a del(11)(q23) by cytogenetics were found to have a t(6;11) (q27;q23), while the other case had a cryptic t(10;11)(q23;q23) with no cytogenetically visible 11q23 abnormality. These observations led Hayette et al to recommend the routine screening of all adults with T-ALL for \textit{MLL} abnormalities.

The European Concerted Action Workshop on 11q23 reported 9 patients with T-ALL and an established 11q23 translocation, with molecular techniques confirming the involvement of the \textit{MLL} gene in 4 cases. The series comprised 3 cases of t(11;19)(q23;p13.3);\textsuperscript{1} 2 of t(10;11);\textsuperscript{2} and one each of t(4;11)(q21;q23),\textsuperscript{3} t(6;11),\textsuperscript{4} t(9;11) (p21~22;q23),\textsuperscript{5} and t(11;17)(q23;q21).\textsuperscript{6} The age of these patients spanned from 3 months to 49 years and consisted of 2 infants (younger than 1 year), 3 children (15 years or younger), and 4 adults.

Since 1998 the Leukaemia Research Fund (LRF) UK Cancer Cytogenetics Group (UKCCG) Karyotype Database in ALL\textsuperscript{5} has been screening patients entered into the Medical Research Council (MRC) ALL treatment trials for abnormalities of the \textit{MLL} gene by interphase FISH. Currently, a total of 210 patients with T-ALL have been screened using commercially available probes: the LSI MLL probe (Vysis, United Kingdom) or the MLL DNA probe (Appligene Oncor, United Kingdom). Overall, rearrangements of the \textit{MLL} gene were found in 10 (5\%) cases. The incidence among children and adults was very similar—7 of 159 (4\%) and 3 of 51 (6\%), respectively. Six cases had a t(11;19), of which 5 were also
observed by G-banded cytogenetic analysis. The remaining 4 cases had cytogenetically visible rearrangements of 11q23, which have not yet been fully characterized. Unfortunately, the follow-up time on these 10 cases is too short to be informative.

Clearly, 11q23/MLL translocations are a recurrent feature of both adult and childhood T-ALL. Although most major 11q23 translocations have been reported in T-ALL, the results from this study and a recent international collaboration suggest that t(11;19) may be associated with T-ALL. Traditionally, 11q23 abnormalities have been associated with a poor outcome, however, recent studies suggest that the worst prognosis is restricted to older adults and infants. Assessing the prognostic significance of 11q23/MLL abnormalities within the context of T-ALL, which is also an indicator of poor prognosis and itself independent of age, will be difficult. Furthermore, the prognostic relevance of different 11q23 translocations has yet to be determined. Therefore, we would strongly recommend screening all subtypes of ALL at all ages for 11q23/MLL abnormalities.

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References


To the editor:

Megakaryocytes from chronic myeloproliferative disorders show enhanced nuclear bFGF expression

Chronic myeloproliferative disorders (CMPDs) comprising chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocytemia (ET), and chronic idiopathic myelofibrosis (IMF) differ in their potential for resulting in bone marrow fibrosis. In IMF, fibrosis usually starts developing in close vicinity to clusters of proliferating and enlarged atypical megakaryocytes. Megakaryocyte-derived basic fibroblastic growth factor (bFGF) has been implicated in the pathogenesis of bone marrow fibrosis in IMF. Different isoforms of bFGF exist and stimulate target cells via membrane receptor or nuclear binding. Distinct biologic functions, depending on the subcellular location of the bFGF species generated, have been described, whereby the nuclear isoform is associated with growth and proliferation.

In an immunohistochemical study of bone marrow trephines, all or at least a considerable proportion of megakaryocytes in PV (n = 10), ET (n = 10), and IMF (n = 19), including the prefibrotic stage (n = 10), exhibited a strong nuclear bFGF expression exceeding that of all other bone marrow cells except endothelium. By contrast, megakaryocytes in CML (n = 10) and controls with reactive megakaryocytic hyperplasia (n = 10) showed no or merely a weak nuclear positivity that did not exceed that of the precursors of the myeloid or erythroid lineage (Figure 1). Fewer than 10% of the non-CML CMPD cases did not exhibit nuclear labeling of megakaryocytes, and a nuclear staining similar to that observable in a minority of lower-expressing CMPD cases occurred exceptionally in one of the reactive control cases.

Because the enhanced nuclear decoration of megakaryocytes could be due to either uptake of bFGF secreted by other bone marrow cells or to autocrine expression, we investigated bFGF mRNA in megakaryocytes by real-time transcriptase-polymerase chain reaction (RT-PCR). Total RNA was extracted and reversely transcribed to 50 from 100 megakaryocytes per case isolated by laser-microdissection (P.A.L.M., Woelfratshausen, Germany) from tissue sections of bone marrow. After linearity of PCR amplification over a broad concentration range and equal efficiencies for all primers/probe systems could be shown, relative quantification of bFGF and β-glucuronidase (β-GUS) mRNA was performed in 2 independent runs using the ΔΔCT-method. Megakaryocytes from PV, ET, and prefibrotic and fibrotic IMF displayed exaggerated bFGF mRNA levels compared to megakaryocytes from normal or reactive controls and CML (P < .0001, respectively). Interestingly, the highest amount of bFGF mRNA was found in megakaryocytes from PV and not in those derived from fibrotic IMF (Figure 2).

We conclude that nuclear overexpression of bFGF characterizes megakaryocytes from PV, ET, cellular and fibrotic IMF and, in most instances, discriminates these diseases from CML and reactive controls. The increased presence of nuclear-detectable bFGF is most likely due to growth factor production by
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