findings support the hypothesis of an important role of angiogenesis in AML. Therefore, we disagree with the authors of the letter that information on well-known prognostic factors is essential for the significance of our findings.

Indeed, we investigated whether bone marrow angiogenesis at diagnosis predicts response to induction chemotherapy. For this purpose, a subgroup of 45 patients was chosen. This group was selected because these patients did not have secondary AML, did not die during treatment-induced bone marrow hypoplasia, and received standard induction chemotherapy.[2] Microvessel counts in bone marrow biopsies at presentation were slightly higher in specimens from patients not achieving a complete remission after induction chemotherapy, as compared with those achieving a complete remission. But the difference was not statistically significant ($P = .147$). Thus, hitherto there is no evidence from our data that the degree of angiogenesis is of prognostic value. Therefore, we did not yet analyze the relationship of microvessel density with known adverse prognostic factors such as unfavorable karyotype or a white blood cell count greater than 20.0×10^9/L.[3]

We fully agree with Drs Reddy and Moreb that it is important to evaluate whether increased angiogenesis is an independent prognostic factor in AML, as it has been demonstrated for various solid tumors. The lack of statistical significance in our report may be due to the small number of patients who did not achieve a complete remission after induction chemotherapy (n = 12). Therefore, we further pursue this question by studying additional patients for known adverse prognostic factors and will report on this. Furthermore, we are in progress of analyzing the prognostic value of microvessel density at presentation for event-free and overall survival. As long as the prognostic value of the degree of angiogenesis has not been demonstrated in AML, we do not see any role for routine determination of microvessel density or even stratification for experimental therapeutic approaches.

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To the editor:

Alopecia and dalteparin: a previously unreported association

Alopecia has not been reported as a side effect of dalteparin. We report the case of a 9-year-old girl who was treated with dalteparin sodium (Pharmacia and Upjohn, Rydalmere, Australia) for sinus venous thrombosis and experienced alopecia that improved on withdrawal of the drug.

The patient presented with headache, neck stiffness, and photophobia in the setting of bilateral otorrhea. Examination showed an unwell girl with an obvious right-sided VIth nerve palsy. Fundoscopy showed blurring of optic disc margins bilaterally. The patient was commenced on IV antibiotics and a performed CT scan demonstrated extensive erosion of the right middle ear and mastoid process associated with right transverse/sigmoid sinus thrombosis. A lumbar puncture showed a cerebrospinal fluid (CSF) opening pressure of greater than 35cm H_2O. No bacterium was isolated on routine culture. The patient had a right-sided cortical mastoidectomy, open removal of thrombus from the sigmoid sinus, and drainage of a perisinus abscess. An ultrasound of the neck showed a complete occlusion of the right internal jugular vein, with thrombus extending to the junction of internal jugular and subclavian veins. The patient was commenced on dalteparin at 100 U/kg given subcutaneously twice daily and monitored with weekly anti-Xa assays. Coumarin was not considered for our patient because of the need for regular therapeutic lumbar punctures. Dalteparin was ceased 24 hours before each lumbar puncture and recommenced 12 hours later. The medications to which the patient was exposed during her inpatient stay included third-generation cephalosporins, natural and synthetic penicillins, aminogylcosides, metoclopromide, paracetamol, and ibuprofen. The patient tolerated further definitive ENT (ear, nose, and throat) surgery without complication. Six weeks after presentation, the patient's eye movements had returned to normal, and audiology showed a moderate conductive hearing loss.

Ten weeks after starting dalteparin, the patient experienced rapid extensive hair loss (see Figure). Examination showed patchy areas of nonscarring alopecia among areas of normal hair growth. The hairs shed were normal in appearance. The patient had been completely well for one month and, apart from dalteparin, had not had any medication for approximately 3 weeks. A repeat ultrasound failed to demonstrate any blood flow within the right jugular vein. In the setting of an improved clinical state and with the onset of alopecia, the dalteparin was ceased. The hair loss improved over the next 2 weeks.

Sinus venous thrombosis in children is an infrequent complication of otitis media and mastoiditis and has been the subject of 2

Alopecia secondary to dalteparin.

recent reviews.[1, 2] Randomised controlled trials in adult patients have shown an improved neurological outcome with anticoagulation.[3,4] A 1999 analysis by de Veber of 150 childhood cases of sinus venous thrombosis showed a decrease in neurological morbidity in the 14 patients treated with anticoagulation.[5] The optimal type and duration of anticoagulation in children with sinus venous thrombosis is unknown.[6]

The prolonged use of low-molecular-weight heparin in our patient had advantages of a minimal need for monitoring and ease of withdrawal of anticoagulation when required for repeated therapeutic lumbar punctures. The side-effect profile of the low-molecular-weight heparin dalteparin is similar to unfractionated heparin, but until this report, alopecia has apparently not been reported (personal correspondence from Pharmacia Upjohn and extensive search of literature). Unfractionated heparin and all other anticoagulants are known to cause alopecia, but the mechanism of hair loss is unknown.[7,8]

Drug-induced alopecia results from either an abrupt cessation of the normal growth phase (anagen effluvium) or a premature transformation of growing hairs into the resting phase (telogen effluvium).[7] Anagen effluvium results in rapid loss of dystrophic hairs and is commonly seen during treatment with chemotherapy. Telogen effluvium, however, leads to hairs being shed 6 weeks to 3 months after drug exposure. Because hair loss is delayed, the alopecia may be difficult to assign to a certain drug exposure. Our patient received 5 doses of oral ibuprofen and intravenous gentamicin, both of which have been associated with alopecia.[8] But based on the well-established association of alopecia and anticoagulants and the timing of the hair loss, we believe dalteparin was the causative agent for hair loss in our patient.

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To the editor:

Accurate quantification of minimal residual disease at day 15, by real-time quantitative polymerase chain reaction identifies also patients with B-precursor acute lymphoblastic leukemia at high risk for relapse

We read with interest the report of Panzer-Grümayer et al[1] in which the authors showed that evaluation of minimal residual disease (MRD) in childhood acute lymphoblastic leukemia (ALL) by semiquantitative molecular methods on day 15 of induction therapy can be implemented in their recently established MRD-based stratification. The authors were able to identify after only 2 weeks of treatment a patient population of 20% who may benefit from the least-intensive treatment. But for patients with higher levels of day 15 MRD (greater than or equal to 10^{-2} or 10^{-3}), only the MRD-based risk groups as defined by later time points were predictive.

We performed a quantitative analysis of MRD by means of the real-time quantitative PCR (RQ-PCR). This approach is far more accurate than semiquantitative analysis of MRD, which was used by Panzer-Grümayer et al.[1] We studied 17 children with B-precursor ALL treated according to protocol VIII of the Dutch Childhood Leukemia Study Group (DCLSG) in the Emma Children's Hospital/AMC (Amsterdam, Netherlands). Immunophenotyping and cytogenetic analysis were performed at diagnosis and relapse, according to standard techniques. Nine patients were in continuous complete remission (CCR), and 8 patients had relapsed (follow-up of at least 60 months after diagnosis). All patients received the same induction therapy. Bone marrow samples of all patients, taken at day 15, at the end of induction therapy and before consolidation, were analyzed for MRD with *IGH*- and *TCRD*- rearrangements as PCR targets. For quantification of residual disease, patient-specific forward primers complementary to the junctional region, in combination with consensus reverse primers and consensus Taqman probes (J_H probes for *IGH* rearrangements and Dδ3-probe for Vδ2Dδ3 rearrangements), were used as described earlier.[2]

Results of MRD levels obtained with RQ-PCR at the 3 time points are shown in the Table. We found a significant difference between MRD levels at day 15 of the patients in CCR, compared with the relapsed patients ($P < .05$). MRD levels after 15 days of chemotherapy were in the CCR group in the range of 0%-1.9%, with one patient negative. For the patients who suffered from relapse, the MRD levels at this time point were significantly higher (2.6%-73%). In agreement with Panzer-Grümayer et al,[1] all patients with rapid molecular response at day 15 (MRD level less than 10^{-4}) are still in CCR. But in contrast to their results, we were able to identify also patients at high risk for relapse. With the quantitative RQ-PCR, it is possible to differentiate patients with relatively high tumor loads, and our results suggest that this accurate quantification is necessary for the identification for patients at high risk of relapse. There is also a clearly significant difference in MRD levels at the end of induction therapy for the