lineages in this species and provided the necessary background for the identification of mouse basophils as interleukin-4 (IL-4)-producing, high-affinity FcR-positive, histamine-containing cells sorted from mouse bone marrow and spleen, previously referred to as non-B, non-T cells.\textsuperscript{10} The ultrastructural characteristics of these basophils are described and contrasted with those of FcR-negative mast cells and with FcR-negative neutrophils and eosinophils in detail.\textsuperscript{4} Further ultrastructural studies with this model revealed that mouse basophils are FcR-positive and c-kit-negative, whereas mast cells are FcR-positive and c-kit-positive, and that mouse basophils did not thrive in cultures supplemented with interleukin-3 (IL-3) or stem cell factor (SCF), on the one hand, or with a combination of these 2 mouse mast cell growth factors, on the other.\textsuperscript{5} In all of these references,\textsuperscript{2-5} ultrastructural images of mouse basophils identical to the basophil in Verbeek et al’s figure 1A-B are included.

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To the editor:

Prognostic correlation of increased angiogenesis in acute myeloid leukemia with cytogenetics

We read with interest the article on the evidence for increased angiogenesis in the bone marrow of patients with acute myeloid leukemia (AML).\textsuperscript{1} The observation that increased microvessel density in the bone marrow may play a role in the pathogenesis and thus be a target for future antiangiogenic therapies is promising. But the article lacks the following important prognostic information to accurately predict the significance of their findings. Their study did not take into account well-documented independent prognostic features of AML currently utilized in predicting a response to induction chemotherapy: (1) unfavorable karyotype and (2) white blood cell (WBC) count greater than 20 $\times$ 10^9/L at presentation.\textsuperscript{2}

It would be of extreme importance to determine whether or not the finding of increased angiogenesis adds to the above mentioned adverse prognostic indicators. In particular, we would like the authors to clarify the relationship of increased microvessel density to cytogenetic findings. Did the 25% of patients who had the 2- to 3-fold increase in angiogenesis belong to a good prognostic cytogenetic group such as inv(16), t(8:21), or the well-known favorable karyotype of t(5;17) relating to acute promyelocytic leukemia?\textsuperscript{3} Stratification of results based on favorable, intermediate, or poor prognostic features would be of importance to analyze if increased angiogenesis is an independent prognostic factor.

Clarification of these findings will help determine whether markers of angiogenesis should be utilized in routine diagnosis of AML and will add to the already-known prognostic markers that predict response to therapy. Such information will allow stratification of patients at their initial diagnosis to determine whether or not they should receive conventional chemotherapy alone or should be considered candidates for high-dose therapy followed by stem-cell transplantation or additional experimental approaches, including antiangiogenic therapies.

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Response:

Angiogenesis and prognosis in acute myeloid leukemia

In their letter, Drs Reddy and Moreb have apparently interpreted our data as indicating that increased angiogenesis is an adverse prognostic factor in acute myeloid leukemia (AML).\textsuperscript{1} But we did not conclude this from our study. Our investigation has unequivocally demonstrated a significant increase of bone marrow microvessel density in 62 patients with newly diagnosed, untreated AML, as compared with control patients. The bone marrow of 75% of the patients (not 25% as stated by Drs Reddy and Moreb) with AML showed a 2- to 3-fold higher microvessel count than the median of the control group. Furthermore, after induction chemotherapy, we observed a significant decrease in microvessel density on day 16 and in complete remission compared with presentation. These

References

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. 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 $20 \times 10^9/\text{L}$. 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 $20 \times 10^9/\text{L}$. 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 $20 \times 10^9/\text{L}$.

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.

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 35 cm H$_2$O. 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 with 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 recommended 12 hours later. The medications to which the patient was exposed during her inpatient stay included third-generation cephalosporins, natural and synthetic penicillins, aminoglycosides, metoclopramide, 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 audiolog 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

References


Alopecia secondary to dalteparin.
Prognostic correlation of increased angiogenesis in acute myeloid leukemia with cytogenetics

Vijay Reddy and Jan Moreb