To the editor:

Vascular endothelial growth factor inhibition is not an effective therapeutic strategy for relapsed or refractory multiple myeloma: a phase 2 study of pazopanib (GW786034)

Vascular endothelial growth factor (VEGF) stimulates plasma cell proliferation and migration in vitro, and preclinical studies have demonstrated that these effects can be blocked by inhibition of VEGF receptors (VEGFRs) in multiple myeloma (MM) cell lines.[1] Pazopanib (GW786034), an oral angiogenesis inhibitor targeting VEGFR, platelet-derived growth factor receptor (PDGFR), and c-Kit, has demonstrated antitumor activity in clinical studies in patients with renal cell carcinoma (RCC), ovarian and related cancers, and soft tissue sarcoma (STS).[2-5] In preclinical models, the in vivo activity of pazopanib was dependent on achievement of a steady-state concentration of at least 40 μM (~ 17 500 ng/mL).[6] A similar steady-state trough plasma concentration (15 000 ng/mL) was associated with biologic and clinical effects after administration of pazopanib in a phase 1 study in patients with solid tumors.[2]

This phase 2 study was conducted to evaluate the safety and efficacy of pazopanib (800 mg daily) in adult patients with relapsed and refractory MM. Eligible patients had measurable levels of M-protein (urine or serum). The primary objectives of the study were clinical efficacy (tumor response rate [RR]), safety, and tolerability. Secondary objectives included time to tumor progression (TTP), time to response, duration of response, pharmacokinetic (PK) profile, and effects of pazopanib on biomarkers of angiogenesis. Approval for these studies was received from each institution's Institutional Review Board and informed consent was obtained in accordance with the Declaration of Helsinki.

Table 1. Baseline patient demographics

Characteristic	Patients (n = 21)
Median age, y (range)	59.0 (29-74)
Male, n (%)	16 (76)
Baseline SWOG stage of MM, n (%)	
1	7 (33)
2	8 (38)
3	5 (24)
4	1 (5)
Baseline ECOG performance status, n (%)	
0	14 (67)
1	5 (24)
2	2 (10)
Prior therapies, n (%)	21 (100)
Stem cell transplantation	15 (71)
Autologous transplantation	13 (62)
Allogenic transplantation	2 (10)
Systemic therapy	21 (100)
Dexamethasone	19 (90)
Cyclophosphamide	16 (76)
Melphalan	15 (71)
Vincristine	14 (67)
Thalidomide	13 (62)
Doxorubicin	11 (52)
Prednisolone	8 (38)
Bortezomib	6 (29)
Doxorubicin hydrochloride	6 (29)
Carmustine	3 (14)
Interferon	3 (14)

SWOG indicates Southwest Oncology Group; MM, multiple myeloma; and ECOG, Eastern Cooperative Oncology Group.

Twenty-one patients received at least 1 dose of pazopanib, with duration of treatment ranging from 1 to 279 days and a median exposure of 64 days. Two patients were excluded from the efficacy analysis: 1 patient violated study eligibility criteria and was withdrawn after receiving 1 dose of pazopanib; a second patient experienced an adverse event (AE) and was withdrawn before the first scheduled disease assessment. All patients had received extensive prior systemic therapy (see Table 1 for patient characteristics).

Sixteen (76%) patients received pazopanib 800 mg throughout the study; median exposure of these patients to treatment was 64 days (range, 1-279 days). Nausea, fatigue, and hypertension were the most frequently reported drug-related AEs. Hypertension was reported as an AE for 6 (29%) patients (grade 1 /2); 5 were considered drug-related. Patients were considered evaluable for efficacy if they completed 6 weeks of treatment and had at least 2 clinical assessments or, if they experienced disease progression, within the first 6 weeks. Nineteen patients were evaluable for efficacy. No patients achieved a partial or complete remission. At the time of the first response assessment at week 6, 9 patients had no change, and 10 patients had progressive disease at or before week 6. Median TTP was 52 days (range, 14-274 days in 15 patients for whom progression data were available). Because no clinical responses were observed, the study was terminated per protocol design.

Plasma pazopanib C_{24} values in 7 of the 11 patients with available PK data were similar to the target concentration (17 500 ng/mL) that has demonstrated anti-VEGF effects in preclinical models.[19] The lack of efficacy observed in patients with MM in this study is therefore unlikely to be attributed to low plasma pazopanib concentrations. Moreover, in this study, patients demonstrated "clinical pharmacodynamic effects" of effective tyrosine kinase targeting as evidenced by hair depigmentation and hypertension.[7,8] The lack of activity of pazopanib in patients with MM may therefore be attributed to the intrinsic biology of the disease. It is noteworthy that the preclinical evaluation of pazopanib in MM demonstrated cytotoxicity only in xenograft models lacking human cytokines. The results of this trial are consistent with data from earlier trials of VEGFR inhibitors (SU5416 and ZD6474) in MM, which also failed to produce any meaningful clinical responses with single-agent regimens.[9,10] Thus, further attempts at VEGF inhibition in MM patients should be approached with caution and need to be based on a strong rationale.

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Contribution: H.M.P. conceptualized and designed the study, provided study materials or patients, analyzed and interpreted the data, and wrote the paper; D.H., A.S., D.A.R., E.A.S., A.W.R., G.T., D.J.D., A.B.S., K.L.B., and L.N.P. provided study materials or patients, analyzed and interpreted data, and wrote the paper; N.B. provided study materials or patients; and B.B. analyzed and interpreted data and wrote the paper.

Conflict-of-interest disclosure: B.B., D.J.D., A.B.S., K.L.B., and L.N.P. are employees of GlaxoSmithKline (GSK; Research Triangle Park, NC). N.B. is a consultant for and has received honoraria from Celgene (Summit, NJ) and OrthoBiotech (Bridgewater, NJ) and has received research funding from Celgene. D.A.R. has received honoraria and research funding from GSK. The remaining authors declare no competing financial interests.

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To the editor:

Neutropenia in congenital nephrotic syndrome of the Finnish type: role of urinary ceruloplasmin loss

Mechanisms for neutropenia are diverse and incompletely understood. Copper is an essential mineral that is absorbed in the intestine, bound to a carrier protein, transported to the liver, and then stored. Approximately 95% of copper found in the blood is bound to ceruloplasmin. Animal models have demonstrated that profound nutritional copper deficiency results in severe neutropenia due to granulopoeisis maturation arrest.[1] In humans, copper deficiency has been reported almost always in patients with chronic intestinal dysfunction, often including gastrostomy, resulting in severe copper malabsorption and frequently anemia, neutropenia and dysmyelopoietic features.[2] It is noteworthy that copper deficiency related neutropenia can be related to anti–neutrophil antibodies.[3] Copper deficiency may worsen anemia in patients with kidney failure[4]; however, it has never been observed in relation to nephrotic proteinuria responsible for urinary ceruloplasmin loss.

The patient was born at 37 weeks gestational age. General edema was present at birth for which congenital nephrotic syndrome (CNF) of the Finnish type was suspected. Renal biopsy showed normal glomeruli and dilated tubuli, and genetic analysis revealed a composite heterozygote mutation in the *NPHS1* gene (c.802C>T; exon 7 and c.2212 + 2delTG; exon 16) coding for nephrin. Massive proteinuria is generally seen in CNF, requiring high-dose intravenous albumin and immunoglobulin supplementation. In our patient proteinuria was exceptionally high (~150 g/L) and the patient required higher doses of albumin (10 g/kg) to keep serum albumin level greater than 20 g/L.

At the age of 2 months, anemia (Hb 6.5 gr/dL) and neutropenia (280/mm^3) were detected, while platelet and lymphocyte count remained normal. There was no clinical or biologic evidence for infection. An infectious work-up, including EBV, CMV, and parvovirus B19 polymerase chain reaction was negative. Anti–neutrophil antibodies were negative. Bone marrow biopsy showed a moderate leukocyte maturation arrest mainly at the myelocyte level and rare megakaryocytes. We measured total copper serum level that was low (3.5 μM; normal range, 12-25 μM); ceruloplasmin level was decreased (0.07 g/L) due to urinary loss of the 135-kDa ceruloplasmin.

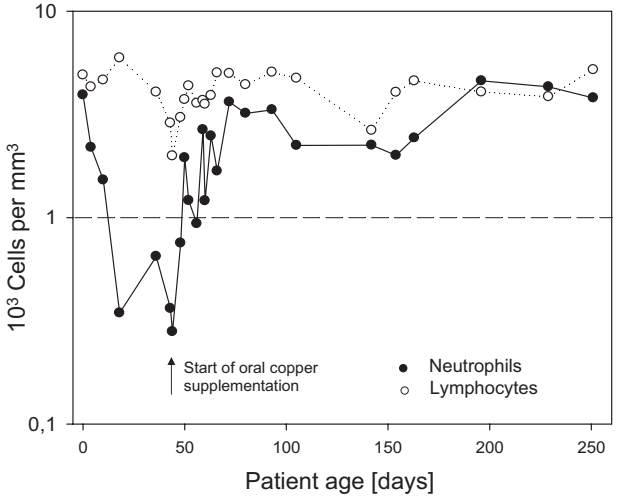

Figure 1. Neutrophil and lymphocyte levels in infant CNF patient.

Oral supplementation of copper sulfate was started at 10 mg per day while white blood cell count and copper serum levels were monitored closely. During copper supplementation, neutrophil count increased and reached an almost normal level of 752/mm^3 (ANC) after 8 days, completely normalized 1 week later, and remained stable (Figure 1). Total copper serum level remained low, as 95% of total copper is bound to ceruloplasmin. However, increase of free copper was correlated to a normalization of neutrophil count, whereas anemia persisted. Anemia refractory to erythopoetin (until 600 U/kg), iron, and vitamin B12 suplementation persisted and was later explained by urinary loss of transferrin and transcobolamin. This second aspect in relation to extremely high proteinuria is reported elsewhere.[5]