References

[1] ten Bokkel Huinink W, Gore M, Carmichael J, Gordon A, Malfetano J, Hudson I, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. J Clin Oncol 1997;15:2183–93.

[2] Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: A randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19:3312–22.

[3] Gordon AN, Tonda M, Sun S, Rackoff W, on behalf of the Doxil Study 30–49 investigators. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. Gynecol Oncol 2004;95:1–8.

[4] Tanner M, Isola J, Wiklund T, Erikstein B, Kellokumpu-Lehtinen P, Malmström P, et al. Topoisomerase IIα gene amplification predicts favorable treatment response to tailored and dose-escalated anthracycline-based adjuvant chemotherapy in HER-2/neu-amplified breast cancer: Scandinavian Breast Group Trial 9401. J Clin Oncol 2006;24:2428–36.

[5] Villman K, Sjöström J, Heikkilä R, Hultborn R, Malmström P, Bengtsson NO, et al. TOP2A and HER2 gene amplification as predictors of response to antthracycline treatment in breast cancer. Acta Oncol 2006;45:590–6.

[6] Mano MS, Awada A, Di Leo A, Durbecq V, Paesmans M, Cardoso F, et al. Rates of topoisomerase II-alpha and HER-2 gene amplification and expression in epithelial ovarian carcinoma. Gynecol Oncol 2004;92:887–95.

[7] Isola J, Tanner M, Forsyth A, Cooke TG, Watters AD, Bartlett JMS. Interlaboratory comparison of *HER-2* oncogene amplification as detected by chromogenic and fluorescence *in situ* hybridization. Clin Cancer Res 2004;10:4793–8.

[8] Di Leo A, Gancberg D, Larsimont D, Tanner M, Jarvinen T, Rouas G, et al. HER-2 amplification and topoisomerase IIα gene aberrations as predictive markers in node-positive breast cancer patients randomly treated either with an anthracycline-based therapy or with cyclophosphamide, methotrexate, and 5-fluorouracil. Clin Cancer Res 2002;8:1107–16.

Motesanib diphosphate (AMG 706), an oral angiogenesis inhibitor, demonstrates clinical efficacy in advanced thymoma

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To the Editor

In May 2000, a 23-year-old male underwent thymectomy and adjuvant radiotherapy for Masaoka stage II thymoma with positive resection margins. In December 2003, CT and positron emission tomography (PET) showed biopsy-proven bilateral pleural recurrence. Left-sided surgical pleurodesis was followed by four cycles of CAP chemotherapy (cisplatin, doxorubicin, cyclophosphamide) with complete remission on CT and PET. However, bilateral pleural disease recurred in March 2005, and he received four cycles of ChlVPP chemotherapy (chlorambucil, vinblastine, procarbazine and prednisolone) and radiotherapy to the left chest wall and diaphragm. Residual disease was seen on CT and PET and he pursued non-conventional therapies over the next 12 months.

Upon return in September 2006, he had multiple new pulmonary nodules and progressive pleural disease. In June 2007 there was significant pulmonary and pleural progression, and he was enrolled onto a phase IB study of motesanib diphosphate (AMG 706) in advanced solid tumours. Motesanib diphosphate is a novel oral, highly specific inhibitor of vascular endothelial growth factor receptor-1 (VEGFR-1), VEGFR-2, VEGFR-3, Kit and platelet-derived growth factor receptor (PDGFR).

The patient received 75 mg of motesanib diphosphate twice daily in three week cycles (two weeks on treatment, one week off). He had stable disease by RECIST (Response Evaluation Criteria in Solid Tumours), although there was a modest increase in tumour measurements that reached a maximum after 11 cycles (January 2008). Subsequently there

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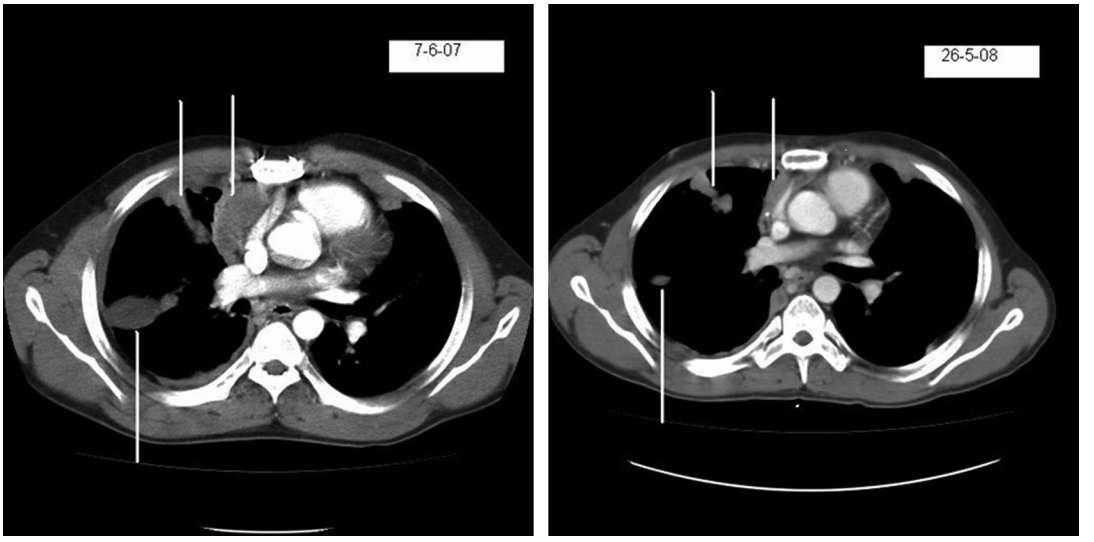

Figure 1. CT scans done at baseline (7/6/07) and after 17 cycles (26-5-08) of treatment with motesanib diphosphate showing reduction in pleurally-based masses.

was improvement, and after 17 cycles (May 2008) there had been a 28% decrease in tumour measurements from maximum (see Figure 1). He remains on study as of July 2008, having received motesanib diphosphate for over 12 months.

Vascular endothelial growth factor-A (VEGF-A) and VEGFR-1 & 2 are uniformly expressed in both normal and malignant thymic tissue [1]. Despite this, there is a paucity of data regarding anti-angiogenesis agents in advanced thymic epithelial tumours. Combined treatment with bevacizumab 15 mg/kg q3w and erlotinib 150 mg/day was evaluated in a phase II trial of 18 patients with recurrent thymic epithelial tumours [2]. No patients achieved a response, but 11 of 18 (60%) had stable disease. In a phase 1 study of escalating doses of aflibercept, a soluble decoy receptor that binds VEGF-A, and docetaxel 75 mg/m^2, one patient with thymoma achieved a partial response [3]. Two patients with thymoma also had a partial response in a phase I trial of SU014813, an oral inhibitor of VEGFR2, PDGFR, Kit, and Fms-related tyrosine kinase 3 (Flt-3) [4].

In a previous phase 1, dose-finding study of motesanib diphosphate in 71 patients with advanced solid tumours, five patients (7%) achieved a partial response and 35 (49%) stable disease [5]. Three of the five responders had advanced thyroid cancer. This led to a phase II study of motesanib diphosphate in 93 patients with advanced thyroid cancer [6], in which the response rate was 14%, and stable disease was achieved in 67% of patients. The clinical trial that our patient is enrolled in is still in progress and results are not currently available.

One patient with advanced thymoma was enrolled in the aforementioned phase 1 study of motesanib diphosphate. This patient was a 49-year-old female with chemotherapy-refractory thymoma. She also attained clinical benefit from motesanib diphosphate, having stable disease for eight months while on study.

We present a very rare case of motesanib diphosphate displaying clinical activity in advanced thymoma. In our patient with chemotherapy-refractory disease, motesanib diphosphate achieved a meaningful reduction in tumour measurements. Interestingly, the patient did not have evidence of actual tumour reduction until after 13 cycles (i.e. 39 weeks), illustrating that the benefit of treatment with targeted agents such as motesanib diphosphate can be delayed. While the response to treatment falls just short of a partial response by RECIST, we believe that further evaluation of anti-angiogenesis drugs such as motesanib diphosphate is warranted for chemotherapy-refractory advanced thymic epithelial tumours.

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References

[1] Cimpean AM, Raica M, Encica S, Cornea R, Bocan V. Immunohistochemical expression of vascular endothelial growth factor A (VEGF), and its receptors (VEGFR1, 2) in normal and pathologic conditions of the human thymus. Ann Anat 2008;190:238–45.

[2] Bedano PM, Perkins S, Burns M, Kessler K, Nelson R, Schneider BP, et al. A phase II trial of erlotinib plus bevacizumab in patients with recurrent thymoma or thymic carcinoma. J Clin Oncol 2008;26(Suppl) (Abstract 19087).

[3] Isambert N, Freyer G, Zanetta S, Falandry C, Soussan Lazard K, Fumoleau P. A phase I dose escalation and pharmacokinetic (PK) study of intravenous aflibercept (VEGF trap) plus docetaxel (D) in patients (pts) with advanced solid tumors: Preliminary results. J Clin Oncol 2008;26(Suppl) (Abstract 3599).

[4] Fiedler WM, Giaccone G, Lasch P, Van der Horst I, Brega NM, Raber S, et al. Phase I trial of SU014813 in patients (pts) with advanced solid malignancies. J Clin Oncol (Meeting Abstracts). 2007;25(18 Suppl):3521.

[5] Rosen LS, Kurzrock R, Mulay M, Van Vugt A, Purdom M, Ng C, et al. Safety, pharmacokinetics, and efficacy of AMG 706, an oral multikinase inhibitor, in patients with advanced solid tumors. J Clin Oncol 2007;25:2369–76.

[6] Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. New Engl J Med 2008;359: 31–42.

Flare-up: An often unreported phenomenon nevertheless familiar to oncologists prescribing tyrosine kinase inhibitors

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To the Editor

A 55-year-old woman with cytokine-refractory metastatic renal cell cancer (RCC) was admitted to the emergency room with symptoms of respiratory distress, pleuritic pain and dry cough. The symptoms had developed rapidly over the preceding 48 hours. On admission, she was afebrile, had no angina pectoris or peripheral edema.

A history revealed that 8 years earlier she had undergone right nephrectomy for clear-cell RCC. Five years after the nephrectomy, immunotherapy with interferon-alfa was initiated due to occurrence of lung, bone and liver metastases, local relapse and involvement of the contralateral kidney. Within 9 months of starting interferon-alfa, the disease had progressed. Interleukin-2 was subsequently given as salvage treatment but stopped after 3 months due to intolerance of the drug. Treatment with zolendronic acid for hypercalcemia and bone metastases was also initiated at this time.

The patient was then switched to treatment with the oral tyrosine kinase inhibitor (TKI) sunitinib (SUTENT®) at a starting dose of 50 mg/day on a 6-week cycle, 4 weeks on treatment followed by 2 weeks off treatment (Schedule 4/2). A partial remission according to Response Evaluation Criteria in Solid Tumors (RECIST) was achieved after four 6-week cycles. Adverse events included grade 2 (National Cancer Institute Common Toxicity Criteria; NCI-CTC) arterial hypertension, hand–foot syndrome, mucositis, diarrhea and hypothyroidism, none of which required dose reduction. Zolendronic acid, initiated 3 months before starting sunitinib, was stopped during cycle 6 due to osteonecrosis of the jaw. During the 2-week off treatment period in cycles 8–11, the patient developed periodic bone pain due to bone metastases. We interpreted this finding as "flare-up" of tumor activity due to interrupted exposure to the TKI, and modified the treatment schedule to continuous dosing of sunitinib 37.5 mg/day. Bone pain resolved and the first two computed tomography (CT) scans after switching to continuous dosing (performed after cycles 14 and 16) confirmed a partial response according to RECIST (Figure 1). After cycle 16, débridement of the mandibula was planned due to progression of the symptoms of zolendronic acid-related osteonecrosis of the jaw.

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