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LETTER TO THE EDITOR

Five patients with malignant endocrine tumors treated with imatinib mesylate (Glivec®)

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To the Editor,

There is no established second line treatment for patients with surgically incurable malignant endocrine pancreatic tumors and foregut carcinoids, who have progressed on standard therapy. Studies of new therapies using novel antitumoral mechanisms of action are needed, if the prognosis is to be improved for these patient categories. Expression of PDGF- and c-kit receptors, targets of the tyrosine kinase inhibitor imatinib mesylate (IM), have been observed in tumor cells in patients with endocrine pancreatic tumors (EPT) [1] and lung carcinoid [2]. To study the efficacy and safety of IM, patients with EPT or foregut carcinoid (FC), with expression of these receptors in tumor cells, were enrolled in an open label, non-controlled prospective phase II clinical trial lasting for 6 months. Fifteen patients were planned to be enrolled. All patients had progressive disease on standard therapies at inclusion. Patients were examined before start of treatment, after one week, after four weeks and then every month. Laboratory evaluation, including full blood count and a biochemical profile, was performed every week during the first four weeks, and then every month. Plasma chromogranin A and B were determined at baseline, after one week and then every four weeks. CT scans and SWOG Solid Tumor Response Criteria assesments were performed at baseline, after 4 and 12 weeks and then after 24 weeks or at end of study. Toxicity was assessed using the WHO common toxicity grading scale. All patients gave informed consent prior to their inclusion in the study and the trial was approved by the local ethics review board.

Seven patients with endocrine pancreatic tumor disease or foregut carcinoid disease were included in the study, but only five were treated with IM for more than a month. Only one was stable during the six months that the study lasted, whereas three patients progressed, either at the first evaluation after one month, or later. One patient left the study to undergo surgery of one of her tumors which was increasing in size, although the patient was radiologically stable at that point according to formal criteria. Regarding biochemical response to IM treatment, Chromogranin A levels had increased by more than 50% at the end of the observation period in four of five patients treated with IM for at least 30 days.

The most common adverse effect was development of edemas. IM treatment was temporarily interrupted for seven days in one patient due to an adverse event with hypocalcemia.

Although no statistically significant conclusions can be drawn from the data of this limited patient material it is still important to report the results, in view of the very short list of patients with EPT or FC previously treated with IM within the framework of formal studies. Gross et al. [3], who do not distinguish between carcinoids of midgut and foregut origin, report three patients. In the study by Gross et al., the majority of patients had other categories of endocrine tumors than those included in the present study, e.g. 6/15 had medullary thyroid carcinoma, 4/15 had adrenocortical cancer and 2/15 had pheochromocytoma. No objective response was reported in that study. Yao et al. [4] also report three patients with foregut carcinoids. Most of the patients

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in the study by Yao et al. had carcinoid tumors of midgut origin. That study however also reports seven patients with carcinoids of unknown origin, some of which may of course be FC. A single patient in this study achieved a partial response.

Other phase II trials with IM in malignant disease with mainly negative results regarding patient response to imatinib have been reported for mesothelioma [5], small cell lung cancer [6], metastatic melanoma [7] and for renal cell carcinoma [8].

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References

[1] Fjällskog M-L, Lejonklou MH, Öberg K, Eriksson B, Janson ET. Expression of molecular targets for tyrosine kinase receptor antagonists in malignant endocrine pancreatic tumors. Clin Cancer Res 2003;9:1469–73.

[2] Granberg D, Wilander E, Öberg K. Expression of tyrosine kinase receptors in lung carcinoids. Tumor Biol 2006;27:153–7.

[3] Gross DJ, Munter G, Bitan M, Siegal T, Gabizon A, Weitzen R, et al. The Israel Glivec in Solid Tumors Study Group. The role of Imatinib mesylate (Glivec) for treatment of patients with malignant endocrine tumors positive for c-kit or PDGF-R. Endocr Relat Cancer 2006;13:535–40.

[4] Yao JC, Zhang JX, Rashid A, Yeung S-CJ, Szklaruk J, Hess K, et al. Clinical and in vitro studies of imatinib in advanced carinoid tumors. Clin Cancer Res 2007;13:234–40.

[5] Mathy A, Baas P, Dalesio O, van Zandwijk N. Limited efficacy of imatinib mesylate in malignant mesothelioma: A phase II trial. Lung Cancer 2005;50:83–6.

[6] Soria JC, Johnson BE, Chevalier TL. Imatinib in small cell lung cancer. Lung Cancer 2003;41(Suppl 1):S49–S53.

[7] Wyman K, Atkins MB, Prieto V, Eton O, McDermott DF, Hubbard F, et al. Multicenter Phase II trial of high-dose imatinib mesylate in metastatic melanoma, significant toxicity with no clinical efficacy. Cancer 2006;106:2005–11.

[8] Vuky J, Isacsson C, Fotoohi M, Dela Cruz J, Otero H, Picozzi V, et al. Phase II trial of imatinib (Gleevec) in patients with metastatic renal cell carcinoma. Invest New Drugs 2006;24:85–8.