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Letter to the Editor

Ongoing under-reporting of clinically relevant safety data in phase II studies of tyrosine kinase inhibitors

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Sir,

We read with some concern in the 13 October issue of your journal the report of the outcome of the phase II study of Novello *et al* (2009) on continuous daily sunitinib dosing in patients previously treated with platinum-based chemotherapy for advanced non-small-cell lung cancer. The trial suggests the potential clinical benefit of this multitargeted tyrosine kinase inhibitor in terms of progression arrest and shrinkage of target lesions on fashionable waterfall plots. This showed one objective partial response among 47 patients (2.1%) treated with a continuous dosing of sunitinib. The interpretation of the efficacy signal generated by this trial is hampered by the non-randomised, non-controlled design of the study. The objective response rate did not meet the pre-defined criterion required to reject the null hypothesis, as at least five objective responses would have been required for a positive outcome of the trial.

A considerable number of patients required dose and schedule modifications. Globally, one out of four patients (25%) discontinued treatment due to adverse events, including four who stopped treatment during cycle 1 for side effects, once again illustrating that multi-targeted tyrosine kinase inhibitors should not be considered as an easy-to-administer, convenient alternative to classical chemotherapy, especially not in a pre-treated, often-elderly cohort of patients with highly refractory solid tumours.

The assessment of safety was defined as a secondary end point in this trial, but the type and frequency of laboratory tests for biochemical evaluation of safety performed during the conduct of the trial were not specified by the authors. We note with surprise that patients participating in the study were not routinely screened either for sunitinib-induced thyroid dysfunction or for cardiac toxicity. There is no mention of routine thyroid or cardiac function assessment during sunitinib treatment. In contrast to this, hypothyroidism, first reported by Desai *et al* (2005), is a well-known adverse side effect of sunitinib (Wolter *et al*, 2008a; Torino *et al*, 2009). Remarkably, the authors report symptoms that are possibly attributable to hypothyroidism in a large proportion of their patients, including a 59.6% incidence of treatment-emergent fatigue (17% of the cases that were categorised as grade 3/4 events), but we could not find any information as to whether this was related to thyroid dysfunction. This is a significant issue because such symptoms might be due to sunitinib-induced hypothyroidism and could therefore be reversible with thyroid hormone replacement. Secondly, fatigue can also be related to cardiac failure, which also has recently been reported as an important side effect of sunitinib (Chu *et al*, 2007; Schmidinger *et al*, 2008; Telli *et al*, 2008; DiLorenzo *et al*, 2009). Unfortunately, detailed information on cardiac toxicity is also lacking, but the authors reported that at least one patient died because of treatment-related congestive heart failure.

According to a growing number of publications, if systematically assessed by thyroid hormone determination, thyroid dysfunction is seen in 30 – 60% of patients treated with sunitinib. In some cases thyroid damage can even be irreversible, leading to the need for long-term thyroid hormone replacement therapy (Wolter *et al*, 2008a; Torino *et al*, 2009; Rogiers *et al*, 2010), which, however, should be carefully individualised (Garfield *et al*, 2007) in light of the evidence that L-thyroxine has been shown to be a growth factor in solid cancers acting via a non-genomic mechanism (i.e., through the av beta 3 integrin receptor to activate tumour cell proliferation; Lin *et al*, 2009). The determination of TSH levels in all patients treated with sunitinib at baseline and during treatment, both within and outside of clinical trials, is recommended by most experts in the field (Kollmansberger *et al*, 2007; Bhojani *et al*, 2008). Recently, we have proposed an algorithm in this journal to deal with this problem in daily clinical practice (Wolter *et al*, 2008a). Indeed, Hellevik *et al* (2009) have reported that in a large prospective population ($n = 30\,000$) study of blood thyroid hormone levels in individuals without a prior diagnosis of cancer, a low TSH level was associated with an increased risk for developing lung and prostate cancer – a risk factor that increases with time.

Furthermore, there are preliminary data showing that thyroid dysfunction under sunitinib treatment might be a surrogate marker for clinical outcome (Wolter *et al*, 2008b). In a prospective study of sunitinib-induced thyroid dysfunction in patients with advanced renal cell carcinoma, the median progression-free survival of patients with thyroid abnormalities was 10.3 months, while for those without the abnormalities it was 3.6 months ($P = 0.047$, log rank test). In addition, the group with thyroid dysfunction had a median overall survival of 18.2 months compared with 6.6 months in the euthyroid group ($P = 0.13$) (Wolter *et al*, 2008b). To further explore thyroid dysfunction as a

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possible surrogate marker for efficacy, the determination of TSH might have been important in the above-mentioned study.

In summary, we cannot conclude that the secondary end point of the present study, namely, to assess the safety of sunitinib in this patient population, was entirely met, as at least two important and well-known side effects were not routinely assessed. We recommend that the safety assessment in patients treated with sunitinib and other tyrosine kinase inhibitors should always include thyroid and cardiac function monitoring to avoid under-reporting of adverse events, to adequately manage potentially reversible side effects and to help identify off-target drug effects as a possible surrogate marker for efficacy.

REFERENCES

Bhojani N, Jeldres C, Patard JJ, Perrotte P, Suardi N, Hutterer G, Patenaude F, Oudard S, Karakiewicz PI (2008) Toxicities associated with the administration of sunitinib, sorafenib and temsirolimus and their management in patients with metastatic renal cell carcinoma. *Eur Urol* **53:** 917 – 930

Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, Woulfe K, Pravda E, Cassiola F, Desai J, George S, Morgan JA, Harris DM, Ismail NS, Chen JH, Schoen FJ, Van den Abbeele AD, Demetri GD, Force T, Chen MH (2007) Cardiotoxicity associated with tyrosine kinase inhibitor Sunitinib. *Lancet* **370:** 2011 – 2019

Desai J, Dileo P, Morgan JA, Larsen PR, Chen MH, George S, Jackson J, Baum C, Demetri GD (2005) Hypothyroidism may accompany SU11248 therapy in a subset of patients (pts) with metastatic (met) gastrointestinal stromal tumors (GIST) and is manageable with replacement therapy. *J Clin Oncol* **23:** 16S (abstract 3040)

DiLorenzo G, Autorino R, Bruni G, Carteni G, Ricevuto E, Tudini M, Ficorella C, Romano C, Aieta M, Giordano A, Giuliano M, Gonella A, De Nunzio C, Ruzzi M, Montesarchio V, Ewer M, De Placido S (2009) Cardiovascular toxicity following sunitinib therapy in metastatic renal cell carcinoma: a multicenter analysis. *Ann Oncol* **20:** 1535 – 1542

Garfield D, Hercbergs A, Davis P (2007) Unanswered questions regarding the management of sunitinib-induced hypothyroidism. *Nat Clin Pract Oncol* **4**(12)**:** 674 – 675

Hellevik AI, Asvold BO, Bjoro OA, Romundstad PR, Nilsen TIL, Vatten LJ (2009) Thyroid function and cancer risk: a prospective population study. *Cancer Epidemiol Biomarkers Prev* 18(2): 570–574

Kollmansberger C, Soulieres D, Wong R, Scalera A, Gaspo R, Bjarnason G (2007) Sunitinib therapy for renal cell carcinoma: recommendations for management of side effects. *Can Urol Assoc J* **1:** S41 – S54

Lin HY, Sun M, Tang HY, Lin C, Luidens MK, Mousa SA, Incerpi S, Drusano GL, Davis FB, Davis PJ (2009) L-Thyroxine vs 3,5,3′-triiodo-L-thyronine and cell proliferation: activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase. *Am J Physiol Cell Physiol* **296**(5)**:** C980 – C991

Novello S, Scagliotti GV, Rosell R, Socinski MA, Brahmer J, Atkins J, Pallares C, Burgess R, Tye L, Selaru P, Wang E, Chao R, Govindan R (2009) Phase II study of continuous daily sunitinib dosing in patients with previously treated advanced non-small cell lung cancer. *Br J Cancer* **101:** 1543 – 1548

Rogiers A, Wolter P, de beeck KO, Thijs M, Decallonne B, Schöffski P (2010) Shrinkage of thyroid volume in sunitinib treated patients with renal cell carcinoma - a potential marker of irreversible thyroid dysfunction? *Thyroid* **20**(3)**:** 317 – 322

Schmidinger M, Zielinski CC, Vogl UM, Bojic A, Bojic M, Schukro C, Ruhsam M, Hejna M, Schmidinger H (2008) Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* **26:** 5204 – 5212

Telli ML, Witteles RM, Fisher GA, Srinivas S (2008) Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. *Ann Oncol* **19:** 1613 – 1618

Torino F, Corsello SM, Longo R, Barnabei A, Gasparini G (2009) Hypothyroidism related to TKI: an emerging toxic effect of targeted therapy. *Nat Rev Clin Oncol* **6:** 219 – 228

Wolter P, Stefan C, Decallonne B, Dumez H, Bex M, Carmeliet P, Schöffski P (2008a) The clinical implications of sunitinib-induced hypothyroidism: a prospective evaluation. *Br J Cancer* **99:** 448 – 454

Wolter P, Stefan C, Decallonne B, Dumez H, Fieuws S, Debaere D, Wildiers H, Clement P, Van Oosterom A, Schöffski P (2008b) Thyroid dysfunction is a candidate surrogate marker for efficacy of sunitinib in patients (pts) with advanced renal cell cancer (RCC). *J Clin Oncol* **26:** 15S (abstract 5126)