

A phase II trial of gefitinib in patients with rising PSA following radical prostatectomy or radiotherapy

GREETTA JOENSUU^{1,2,*}, TIMO JOENSUU^{2,*}, NINA NUPPONEN³, MIRJA RUUTU⁴, JUHANI COLLAN⁵, SARI PESONEN^{1,6} & AKSELI HEMMINKI^{1,6}

¹Cancer Gene Therapy Group, Molecular Cancer Biology Program & Transplantation Laboratory & Haartman Institute & Finnish Institute for Molecular Medicine, University of Helsinki, Helsinki, Finland, ²International Comprehensive Cancer Center Docrates, Helsinki, Finland, ³Molecular Cancer Biology Program, University of Helsinki, Helsinki, Finland, ⁴Department of Urology, Helsinki University Central Hospital, Helsinki, Finland, ⁵Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland and ⁶HUSLAB, Helsinki University Central Hospital, Helsinki, Finland

To the Editor,

Prostate cancer recurrence after therapy with curative intent is often first detected as an increase in prostate-specific antigen (PSA) ("rising PSA syndrome") which may occur years in advance of clinical recurrence, and may present an opportunity for effective treatment in the context of minimal disease load. Eventually 5–66% of patients with rising PSA receive salvage therapies, the most common of which are radiation of the prostate basin after surgery and hormonal treatments especially in relapses following radical radiotherapy of prostate [1,2]. Regrettably, although both modalities are effective in many patients, they also cause significant morbidity. Also, radiation is effective only in locally recurrent disease and therefore only 55–72% of rising PSA patients feature PSA response when given salvage radiation [3,4]. Hormonal therapies are initially effective in most patients, but they cause numerous long-term side effects and their benefit is often eventually lost, which results in difficult-to-treat castration resistant prostate cancer (CRPC) [5].

High expression of epidermal growth factor receptor (*EGFR*) has been reported in 41–86% of non-metastatic prostate cancers [6,7]. *EGFR* over-expression and activation are associated with poor prognosis that is manifested by late-stage disease, angiogenesis, metastasis, and resistance to hormonal therapy and radiotherapy. Gefitinib is a potent and selective inhibitor of *EGFR* which has shown anti-tumor effects in Phase I–III studies in patients with various solid tumors, including advanced prostate cancer, but it has not been studied in patients with subclinical disease [8–10]. No benefits were seen in advanced prostate cancer patients treated with gefitinib monotherapy [11]. Nevertheless, given the activity seen in preclinical

model systems, or in combination with radiotherapy or with other antitumor agents, it is conceivable that prostate cancer patients with low tumor load and slowly growing tumors might benefit from gefitinib [12,13]. Therefore, we hypothesized that gefitinib could delay PSA progression, increase PSA doubling time (PSADT) and therefore postpone the need for hormonal or radiation salvage therapy in patients with rising PSA.

This was a single center, non-randomized, open-label Phase II trial. Patients were enrolled between December 2003 and January 2005. The primary objective of the trial was to evaluate the activity of once daily 250 mg gefitinib in hormone naive prostate cancer patients (See supplementary Table I to be found, online at <http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2011.617387>) with rising PSA following radical prostatectomy or radiotherapy with curative intent. Rising PSA was defined as two (after prostatectomy) or three (after radiotherapy) consecutive, independent (at least four weeks apart) PSA increases. PSA was to be < 10 ng/ml and WHO performance status 0–1 was required. All patients were planned to be treated for a minimum of three months.

Since all patients were free of metastases and had only biologically measurable disease, the primary measure of activity was PSA response, defined as the percentage of subjects experiencing PSA normalization or more than 50% reduction of PSA for three months. Secondary objectives were time to treatment failure, duration of PSA response, PSA progression free survival and effect of treatment on PSADT. Tolerability of the treatment was also studied. The final trial protocol, including the final version of the Written Informed Consent Form, was approved by the Helsinki University Central Hospital Surgical Ethics Committee. The trial

*These authors contributed equally.

Correspondence: A. Hemminki, Biomedicum, PO Box 63, 00014 University of Helsinki, Helsinki, Finland. Fax: +358 9 19125465. E-mail: akseli.hemminki@helsinki.fi

was performed according to Good Clinical Practices and the Declaration of Helsinki (clinicaltrials.gov trial identifier, NCT00241475).

The primary endpoint of the study (PSA response) was not met.

Nineteen patients had had a prostatectomy with entry serum PSA values ranging from 0.2 to 4.5 ng/ml whereas the 11 patients treated with radiotherapy had entry values ranging from 1.1 to 8.5 ng/ml. Three months after initiation of gefitinib, seven (23.3%) patients had interrupted the treatment and 23 (76.7%) patients were free from treatment failure (see Supplementary Table III, Figure 1A to be found, online at <http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2011.617387>). The most common causes of treatment failure were PSA progression (five patients, 16.7%) and adverse events (AE) (two patients, 6.7%). Median time on gefitinib treatment was 145.5 days (range 33 to 600 days). Twenty-eight (93.3%) of patients experienced AE potentially related to gefitinib. The most common were gastrointestinal disorders (23 [76.7%] patients), skin and subcutaneous tissue disorders (22 [73.3%] patients) and infections (12 [40%] patients) (see Supplementary Table II to be found, online at <http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2011.617387>). Twelve (40.0%) patients had one or more interruptions of gefitinib dose, which were due to transaminase increase in 11 (36.7%) patients and due to lapse of memory in one (3.3%) patient. No grade 4–5 AE were recorded. One serious AE was recorded however it was eventually scored as grade 1 not related to gefitinib, and it did not led to treatment withdrawal.

By three months, PSA progression was recorded for seven (23.3%) patients and thus 23 (76.7%) patients were progression free (see Supplementary Table III, Figure 1B to be found, online at <http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2011.617387>). Median time to PSA progression was 60 days (range 27–90 days). PSADT could be measured in 27 patients and it decreased in 10 patients, although in eight the decrease was small (less than 50%) compared to the PSADT before gefitinib. However, with 17 patients we observed an increase in PSADT during gefitinib treatment (see Supplementary Figure 2 to be found, online at <http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2011.617387>) and in six patients PSADT increased 100% or more. PSADT change could not be evaluated in three patients since they had only one PSA measurement during treatment.

Recent studies argue that a rapidly rising PSA after local therapy reflects a more urgent need for administration of systemic treatment in comparison to a slowly rising PSA [14,15]. The first choice for

systemic therapy is usually hormonal treatment which is well established in relapsed and metastasized prostate cancer as well as an adjuvant treatment in high-risk prostate cancer. Overall the response rate in hormonal treatment is over 90% but the problem is that castration resistant disease eventually emerges [16]. In a long run the hormonal therapy appears to change the prostate cancer character into more aggressive form in which *EGFR* expression is present in 76–100% of cases [6]. More recently the long-term side effects of hormone therapy have turned out to be quite numerous and also detrimental for quality of life or causing even serious health concerns for otherwise asymptomatic men [5,17]. Therefore, the utility of early hormonal therapy remains controversial and observation is often recommended until a clear PSA or clinical relapse develops [18].

The statistical target for this trial, for proceeding to a randomized phase III trial, was a greater than 40% response rate but this was not achieved. An amendment was made to allow patients without PSA progression to continue therapy for a further three months but, in spite of this, no responses were seen. It might be possible that the dose of 250 mg was too low, however given the toxicities seen already with 250 mg in healthy men, it is difficult to envision going higher. In a study of Canil et al. of two doses of gefitinib in patients with PSA levels of ≥ 20 ng/ml neither 250 mg nor 500 mg led to responses [9]. Similarly Curigliano et al. did not find efficacy of gefitinib in prostate cancer but also in their study the disease was already in CRPC-phase which is probably more resistant to any treatment options [19]. Besides, based on pharmacodynamic studies the inhibition of *EGFR* activation affecting downstream receptor-dependent processes appears to happen profoundly at doses well below the one producing unacceptable toxicity, a finding that strongly supports to select optimal doses instead of a maximum-tolerated dose for definitive efficacy and safety trials [20]. However, in our study the patients were all hormone naive and thus potentially hormone sensitive as well as sensitive to other therapies, whereas in the study of Canil et al. the patients had CRPC which is known to be more aggressive, resistant and difficult to treat. Also, *EGFR* expression was not a prerequisite for enrolment in our study and without the specific *EGFR* tyrosine kinase domain mutations (exons 18–21) in the tumor it is unlikely that gefitinib would be effective [6,7,21]. Therefore, it is possible that only a small proportion of the patients in this study had the possibility of benefiting from gefitinib.

The natural history of recurring prostate cancer after definitive local therapies varies remarkably and is often indolent. In the study of Freedland et al. the PSADT and the time from surgery to PSA relapse were

both significant predictors for time to prostate-specific mortality [22]. PSADTs of less than three months versus over 15 months had a 28-fold difference in risk of death from prostate cancer. Similar outcomes were reported by D'Amico et al. and Albertsen et al. [14,15]. In our study gefitinib appeared to increase the PSADT in most patients which might be enough to postpone clinical relapse and/or initiation of salvage therapy. Although the gefitinib single-agent efficacy was shown to be quite small, the *EGFR* inhibition might still be a potential strategy if combined to other treatment modalities as our own study suggests with definitive prostate cancer radiotherapy [13]. However, it should be noted that our previous study was not randomized. In combination strategies the gefitinib dose could also be decreased without compromising the biological effect diminishing at the same time possible side effects [20].

Since no PSA responses were recorded the primary endpoint of this study was not met. The safety of gefitinib 250 mg daily was manageable with majority of AEs being mild and as expected. Almost two thirds of patients demonstrated an increase in PSADT, suggesting anti-tumor activity, although a reliable outcome can be achieved only with a randomized trial. The single agent activity of gefitinib was small despite an early intervention in biochemical recurrence of prostate cancer before hormonal therapies. Further work is needed to identify how the inhibition of *EGFR* could possibly be combined in the best way to the other prostate cancer treatment options.

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Supplementary material available online

Tables I–III

Figure 1A and B

Figure 2

Sequence analyses of *EGFR* and *KRAS* exons
