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Reasons for initial PSA (iPSA) and biochemical failure (BF) being poor predictors of prostate cancer (PC) mortality

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Background: iPSA and BF are often poor predictors of mortality in men treated for locally advanced PC. We sought to find out why from prospective randomised trial data.
Methods: In the TROG 96.01 trial men with T2b,c, 3, 4 N0 PC were randomised to 0, 3 or 6 months maximal androgen deprivation (AD) (goserelin 3.6 mg sc monthly and flutamide 250 mg po tid) prior to 66 Gy to the prostate and seminal vesicles. Failure site was diagnosed prior to salvage hormone therapy (ST) where possible, and type, timing and duration of response to ST recorded. Proportional hazards modeling was used to identify predictors of cause specific and overall survival (CSS, OS) at follow-up landmark points (where p >0.05 = [NS], <0.01 = [S], <0.001 = [H]).
Results: Between 1996 and 2000, 802 eligible men were randomised. Higher iPSA was found to be a potent predictor of BF (Houston [HF]) [H] but a poor one for of CSS [NS] and OS [NS]. Patients having HF and/or clinical failure had unfavourable initial prognostic factors (high iPSA [H], stage [H], Gleason score [H] or risk group [H]) compared to patients who did not fail. However in this cohort poor initial prognostic features did not predict PC death when the relapse characteristics (failure site [H] and PSA doubling time [PSA DT] [H]) were accounted for. Instead lower iPSA levels were predictive of worse outcome in these models [S], a finding supported by univariate analyses.
PSA DT was found to correlate positively with interval between HF and ST [H] and the likelihood [S] and duration of response to ST [H], and survival [H]. Thus lower PSA DTs were associated with earlier intervention but poorer responses and outcomes.
Conclusions: Prognosis after BF is related more to tumour biology at relapse than to initial prognostic factors. ST alone is an unsatisfactory treatment for rapid PSA DT relapses.

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Avoiding overtreatment of prostate cancer: optimising patient selection for active surveillance

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Background: There is a major unmet need for markers of localized prostate cancer behaviour. We have analysed early outcome data from a prospective study of active surveillance in order to identify factors that would inform the decision whether or not to undergo immediate radical treatment at the time of diagnosis.
Methods: Eligible patients had clinical stage T1/T2a, N0/Nx, M0/Mx adenocarcinoma of the prostate with serum PSA < 15 ng/ml, Gleason score <7, primary Gleason grade <3, and % positive biopsy cores (pbc) <50%. Monitoring included serial PSA measurement and repeat prostate biopsies. Radical treatment was initiated in the event of biochemical progression (PSA velocity >1 ng/ml/year) or histologic progression (primary Gleason grade >4, or %pbc > 50%). Multivariate analysis of clinical variables available at the time of diagnosis was performed with respect to time to subsequent radical treatment.
Results: 326 men were recruited between 2002 and 2006, and have been followed for a median of 22 months. Median age was 67 years, and median initial PSA (iPSA) 6.4 ng/ml. Sixty-five patients (20%) had deferred radical treatment, 16 (5%) changed to watchful waiting due to increasing co-morbidity, 7 (2%) died of other causes, and 238 (73%) remain on surveillance. No patients developed metastatic disease or died of prostate cancer. On multivariate analysis the free/total PSA ratio (p = 0.0002), iPSA (p = 0.002) and clinical T stage (p = 0.02), were independent determinants of time to radical treatment. Based on the multivariate analysis, the cohort was divided into 3 groups based on initial PSA level and free/total PSA ratio. Group 1 had both a PSA less than the median value (6.4 ng/ml) and a free/total PSA ratio greater than or equal to the median (18%); group 2, had one, but not both, of these factors, and group 3 had both a PSA $\geqslant$ 6.4 ng/ml, and a free/total PSA ratio <18%. The actuarial rate of treatment at 3 years was 0%, 27% (95% CI: 17−39%) and 55% (95% CI: 41−71%) for groups 1, 2 and 3, respectively.
Conclusions: In addition to the serum PSA level, the free/total PSA ratio may be a useful marker for disease progression in untreated, localized prostate cancer. This possibility warrants further study. There remains a need for additional biomarkers of prostate cancer behaviour to identify who does, or does not, need treatment. Active surveillance of localised prostate cancer is feasible, with encouraging short-term results.

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An open label randomized Phase II study of oral triple angiokinase inhibitor BIBF 1120 in Hormone Refractory Prostate Cancer (HRPC) patients who progressed after docetaxel

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Background: VEGF, PDGF and FGF receptors compose critical cellular pathways controlling angiogenesis. BIBF 1120 is a novel oral potent triple angiokinase inhibitor targeting VEGFR, PDGFR and FGFR. The aim of the study was to determine the efficacy and the safety of continuous treatment with two different doses of BIBF 1120 in HRPC patients after progression with docetaxel based regimen.
Methods: From 11/ 2005 through 6/ 2006, 81 men (ECOG of 0−2) were included and randomly assigned to receive either 250 mg or 150 mg of BIBF 1120 twice daily. The primary endpoint was response rate defined as a confirmed decline of PSA $\geqslant$ 20%. Secondary endpoints were the rate of decline of PSA $\geqslant$ 50%, the progression free survival, the clinical benefit, and the safety of BIBF 1120.
Results: Both treatment arms were comparable with respect to baseline characteristics. Median age of all patients was 69 years (53 to 85), median number of metastatic sites was 1 (1 to 4), bone lesions in 80/81 patients and median PSA value was 216 ng/mL (18 to 2079). There was no significant difference with respect to PSA response rate between both treatment arms. A 20% PSA response was observed in 6 of 81 patients. Four patients treated with 250 mg bid had a confirmed response and two of them showed a 50% PSA decline. Mixed linear regression analysis of the log PSA-values showed a significant slowing down of the PSA increase during continuous treatment with 250 mg bid in comparison to the PSA increase before start of treatment with BIBF 1120 (p < 0.01). The progression free survival was not different between both treatment arms. One partial response according to RECIST was observed in the 250 mg bid group. The most common BIBF 1120 related adverse events in the 150 mg bid and the 250 mg bid treatment arm were gastrointestinal disorders such as diarrhoea (43% versus 45%), nausea (41% versus 42%), vomiting (22% versus 30%), and asthenia (46% versus 37) of mostly low intensity. Reversible liver enzyme increase of CTCAE grade 2 and 3 have been observed in 2 and 14 patients, respectively.
Conclusions: Continuous treatment with BIBF 1120 was well and safe tolerated. Despite a low response rate, the data suggest that treatment with BIBF 1120 might slow down the velocity of the PSA increase in patients that progressed after docetaxel treatment.