About sorafenib in castration-resistant prostate cancer

In the study design of Chi et al. [1] is declared that sorafenib would be considered of interest if three or more prostate-specific antigen (PSA) responses were observed in the 25 patients accrued. In their trial, a PSA response occurred in one patient among 28 patients treated with sorafenib; therefore, sorafenib should be considered ineffective in chemonaive castration-resistant prostate cancer. The authors concluded that further study may be warranted, but needs to consider the limitations of PSA as an indicator of progression and response. In summary, Chi et al. believe that activity of this drug was missed in such a trial, also considering a recent finding about the effect of sorafenib on PSA [2].

Historically, post-therapy PSA decline has been proposed as a surrogate end point to evaluate new cytotoxic agents in metastatic castration-resistant prostate cancer [3]; PSA decline within 3 months of treatment initiation provided the highest degree of surrogacy for overall survival in a retrospective assessment of TAX327 trial [4] and similar results emerged from an analysis of data from SWOG 99-16 [5].

Criteria for PSA response were prospectively validated with taxanes/epothilones [6] and other drugs [7, 8]. At the same time, the necessity to verify the instrumental response after 4 weeks and PSA response after 12 weeks was pointed out [6]. The post-chemotherapy PSA surge syndrome suggests the opportunity of treatment continuation beyond 8 weeks despite an initial PSA elevation, with the obvious exception of a clinical disease progression [9].

Prostate Cancer Clinical Trials Working Group recommends, for noncytotoxic drugs, shifting the focus of designs from response to time to event end points, suggesting a phase II trial, possibly randomised, with TTP or TTF and not PSA response as primary end point, and that it will be also important keeping patients on trial until radiographic or symptomatic progression is documented [10].

To date, results of two other phase II trials of sorafenib in castration-resistant prostate cancer have been published [11, 12], both evidencing a limited activity of sorafenib. The first paper, additionally, reported a discrepancy between PSA response and clinical response: in this study, two patients with PSA progressive disease experienced a response on bone scan, and six of 17 with PSA progression presented a spontaneous reduction of PSA after suspension of sorafenib;
therefore, a second stage of the trial was planned without PSA response among end points [11].

According to authors, a further phase II trial is necessary; however, some aspects of the present study are missing. First, the clinical subtypes of 26 metastatic patients, on the basis of type of spread as stated by Prostate-Specific Antigen Working Group [13], are not reported; second, it is not specified how many of 62% of ‘late’ PSA reduction were PSA responses; third, it is not clear if similar late declines of PSA were documented in those five patients who stopped sorafenib due to instrumental progressive disease. Finally, the discussion raises the question of how many patients were on androgen deprivation, surgical or chemical, during the trial. Previously, the effect of androgen receptor on PSA expression, through genomic and nongenomic actions, has been described in castration-resistant prostate cancer [14]; a possible reversion of androgen independence through attenuation of ras signalling has been reported [15] and it could be induced by sorafenib. Consequently, whether patients were all on androgen deprivation therapy during the trial, it can be postulated that sorafenib could have restored some hormone sensitivity in responding patients and it could interfere with androgen receptor nongenomic regulation of PSA expression.

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