About tyrosine kinase inhibitors (TKIs) in prostate cancer: where do we go from here?

We read with interest the results of Dror Michaelson et al. [1] regarding a phase II study of sunitinib in men with advanced prostate cancer. The primary objective of the study was to determine whether sunitinib would result in a 50% decline in the prostate-specific antigen (PSA) with a minimum of two responses required in each of the two groups (both chemotherapy naive and docetaxel resistant), in order to proceed to the second stage. The study did not meet its primary end point and while few PSA responses were seen, several patients had clinical and radiographic improvements despite PSA rises. The results are reminiscent of the findings using sorafenib in prostate cancer [2–6], which also led to few PSA declines (Table 1). In the initial analysis of a phase II study using sorafenib for predominantly chemotherapy-naïve patients with metastatic prostate cancer [4], use of an alternative serum biomarker, phosphorylated extracellular signal-regulated kinases (pERK), was explored as a potential biomarker since sorafenib inhibits Raf kinases which are upstream of pERK. However, no consistent reduction in pERK levels was seen. In the sunitinib study, serum biomarkers using soluble vascular endothelial growth factor receptor, among others, demonstrated on-target effects of sunitinib.

Table 1. Phase II sorafenib monotherapy trials in prostate cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Primary end point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi et al.</td>
<td>28</td>
<td>≥50% PSA decrease for 24 weeks</td>
<td>One patient with response (3.6%; 95% confidence interval 0.1% to 18.3%)</td>
</tr>
<tr>
<td>Steinbild et al.</td>
<td>57</td>
<td>PSA progression-free survival of ≥12 weeks</td>
<td>15 patients had stable PSA and 2 had declines of 31%</td>
</tr>
<tr>
<td>Dahut et al.</td>
<td>22</td>
<td>4-month probability of PFS assessed with disease progression either by RECIST or PSA</td>
<td>13 patients progressed by PSA criteria alone; two patients with radiographic improvement despite PSA progression</td>
</tr>
<tr>
<td>Aragon-Ching et al.</td>
<td>24</td>
<td>4-month probability of PFS with assessment of disease progression either by RECIST or clinical criteria alone</td>
<td>One patient had partial response; 10 had stable disease</td>
</tr>
</tbody>
</table>

Partial response is defined as at least a 30% decrease in the sum of the longest diameter of target lesions; stable disease is defined as less than a 30% decrease and less than a 20% increase in the sum of the longest diameter of target lesions.

PSA, prostate-specific antigen.

One begs the question, do the results simply imply that these drugs are of limited activity or are we using the wrong end point? The limitation of PSA as a biomarker is increasingly recognized in the assessment of response to treatment in men with metastatic castration-resistant prostate cancer. Increasingly, there is a movement away from the use of PSA as a sole criterion for measurement of progressive disease. The Prostate Cancer Clinical Trials Working Group (PCWG2) recommends that early changes in PSA, in the absence of other objective disease progression, should not herald a prompt discontinuation of drug therapy [7]. This is particularly applicable in the era of tyrosine kinase inhibitors (TKIs), where PSA changes may not be predictive of radiographic or clinical response and/or benefit. However, there is, as of yet, no candidate biomarker that is ready to replace the PSA. Other adjunctive modalities may therefore have a role. For instance, in a phase II trial using AZD2171, targeted activity on digital contrast-enhanced magnetic resonance imaging correlates with tumor response [8]. Clearly, better imaging techniques would be useful in determining the activity of these agents.

One recently convened workshop on imaging conducted by the National Cancer Institute addressed this issue of assessing response to therapy in advanced disease [9]. In addition, other surrogate end points other than PSA may be considered.

Combinations of TKIs with cytotoxic chemotherapy is the ‘knee-jerk’ next step and is an area of active clinical investigation, but without tools to determine which patients are likely to benefit and a reliable measurement of antitumor activity, results are likely to be difficult to interpret and ultimately disappointing. Although overall survival was not the primary end point in a phase II sorafenib study of both cohorts of patients (chemotherapy naive in stage I and a predominantly docetaxel-pretreated population in stage II) [5], updated analysis showed a median overall survival of 18.3 months, comparable to other cytotoxic regimens [10–13], indicating possible clinical utility.

In conclusion, the dilemma in prostate cancer remains that drugs that ‘may have some activity’ cannot easily be distinguished from drugs with ‘no activity’ using our current biomarkers and imaging. Until we have more active agents or have a better means of selecting patients who are most likely to benefit, we are likely to spend a significant time conducting phase II trials and being forced to make a ‘go/no-go’ phase III decision without the tools we need.

J. B. Aragon-Ching1* & W. L. Dahut2

1Department of Medicine, Division of Hematology–Oncology, George Washington University Medical Center, Washington, DC, 2Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

(*E-mail: jaragonching@mfa.gwu.edu)

disclosure

We have no conflict of interest to declare.
references


doi:10.1093/annonc/mdp467
Published online 10 November 2009