Re: Design and Endpoints of Clinical Trials in Patients with Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group

Expert's summary:
The revised recommendations move away from the “prostate specific antigen (PSA) response” endpoint that was originally proposed [1] for phase II trials, to now recommend time-to-event endpoints, or progression-free survival rate as a more reliable indicator of treatment activity. They also urge that one should not stop (cytostatic) treatments before 12 wk, despite non-decreasing PSA levels or apparent worsening of the bone scans, to ensure sufficient drug exposure. The authors reiterate the need to understand the drug’s mechanism of action on PSA.

Expert’s comments:
The evidence has now accumulated that PSA response is not a good surrogate for survival and should not be the endpoint of phase III trials. Even for phase III trials in progressive hormone independent disease assessing cytotoxic agents such as docetaxel, experts conclude that overall survival should remain the end point for phase III trials [2].

Several recent trials have exemplified the risks of using PSA as endpoint in phase II trials of cytostatic agents. In the ASCENT trial [3], no benefit of high-dose calcitriol was seen on the primary endpoint of PSA response at 6 mo (p = 0.16) nor for biochemical progression-free survival (p = 0.7), despite a significant benefit in survival (p = 0.04) over placebo. In a single arm phase II trial of sorafenib [4], 21 of 22 patients stopped treatment after 8 wk, 17 of whom with PSA-only progression. In vitro studies then showed that the drug increases PSA secretion independent of the antitumour effect.

One must thus applaud the revised guidelines, emphasizing the need to understand the agent’s effect on PSA before launching the trial. ASCENT [3] also shows that moving from PSA response to a time-to-event endpoint that implies PSA is not sufficient, and that truly clinically relevant endpoints must be preferred. Overall survival rate at 6 or 12 mo itself may be a valid phase II endpoint in settings where the median survival is short.

Recognizing that the key problem is not PSA but the difficulty of measuring the disease and most of all its extension into the bones, we can only support further research on the magnetic resonance imaging of the axial skeleton [5]. This technique, which already showed good promise as a diagnostic tool as well as to measure tumour response in the bone, has the potential to bring prostate cancer to the same level as other solid tumours, in regard to the ease of defining endpoints for phase II trials.

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References

Laurence Collette
European Organisation of Research and Treatment of Cancer (EORTC) Headquarters,
Statistics Department, Avenue Emmanuel Mounier 83/11, 1200 Brussels, Belgium
E-mail address: laurence.collette@eortc.be
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Re: Lower Urinary Tract Symptoms in Dementia with Lewy Bodies, Parkinson Disease, and Alzheimer Disease
Ransmayr GN, Holliger S, Schletterer K, Heidler H, Deibl M, Poewe W, Madersbacher H, Kiss G

Expert's summary:
In this study [1] the authors investigated lower urinary tract symptoms (LUTS), frequency volume charts, and urodynamic findings in 15 patients with dementia with Lewy bodies (DLB), 15 with Parkinson disease (PD), and 16 with Alzheimer disease (AD). Urgency, urgency incontinence, and detrusor over-
activity were significantly more prevalent in patients with DLB compared to those with PD and AD. In contrast, 24-h frequency, maximum cystometric capacity, detrusor pressure at maximum flow rate, maximum flow rate, voided volume, and post-void residual were similar in the three groups and corresponded to values in the general elderly population.

**Expert’s comments:**
Urinary incontinence has already been shown to be an early symptom in DLB, whereas in AD it occurs in an advanced stage of the disease [2]. In PD, LUTS deteriorate with duration and progression of motor symptoms [3]. Ransmayr and colleagues [1] compared LUTS and urodynamic findings in different neurodegenerative diseases. Detrusor overactivity was common and found in 92%, 46%, and 40% of the patients with DLB, PD, and AD, respectively. These findings have major implications for urologic treatment: Antimuscarinics are the gold-standard pharmacologic therapy of detrusor overactivity. However, muscarinic receptors are prominent in the central nervous system (CNS) and play an important role in memory, vigilance, problem solving, and stimulus and response processing [4]. Thus, differences in permeability of the blood–brain barrier and in receptor selectivity of the different antimuscarinics have to be considered. Nevertheless, CNS effects of antimuscarinics have been poorly investigated, and, so far, there is no prospective clinical trial in patients with neurodegenerative disease treated for overactive bladder symptoms.

In a postmortem brain morphology study in patients with PD, Perry and colleagues [5] found an increased AD-like pathology in patients with prolonged antimuscarinic exposure. Antimuscarinic treatment of 2 yr or more was associated with significantly increased densities of amyloid plaques and neurofibrillary tangles, compared with those cases with less than 2 yr of drug treatment. This raises the worrying question: Does chronic antimuscarinic therapy increase the risk of AD or accelerate AD pathogenesis?

Does this mean that we should avoid antimuscarinic treatment for overactive bladder symptoms in patients with neurodegenerative disease? Probably not, but we should be aware of potential effects such as precipitating or exacerbating delirium, confusion, and cognitive deterioration, and discontinue the treatment if appropriate. In addition, polypharmacy is very common in this group of patients, and many other drugs have antimuscarinic properties, which make these patients even more susceptible to CNS adverse effects. Thus, well-designed, adequately powered trials in the at-risk population, including neurogenic and older patients, are urgently needed.

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**References**


Thomas M. Kessler
Department of Uro-Neurology,
The National Hospital for Neurology and Neurosurgery,
University College London Hospitals, London, UK
E-mail address: tkessler@gmx.ch

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