Novel therapies for advanced prostate cancer: have we have widened the goal posts too far?

In the past 25 years, the nature of advanced prostate cancer trials has changed substantially. The modern era of clinical trials for this vexing disease was heralded by the early work of the National Prostate Cancer Project in the United States, which attempted to structure its studies based on an innovative system that focused on careful documentation of the extent of disease, and the concept that effective treatment would either cause objective response (complete or partial) or could halt the progression of disease by establishing a stable state [1]. The problem with this approach was the lack of a reliable biomarker and the failure to address the fact that many cases of advanced prostate cancer are indolent, with very slow progression, and that an apparently stable state might be present prior to the initiation of the novel chemotherapy (thus negating the biological impact of this treatment) [2, 3].

The principle that stable disease was a useful response criterion for advanced prostate cancer trials fell from grace in the 1980s, and was replaced by a greater focus on changes in the symptomatic state, more refined criteria of objective response, and the linkage of survival figures to other reporting indices. Thus phase II studies of (then) novel hormonal agents and cytotoxics focused on changes in levels of pain, performance status, weight loss, constitutional features, objective response in soft-tissue disease in particular, with associated reporting of survival [4–8]. Similar indices became the outcome measures in many phase III trials of that era [9]. However, these studies were also beset by the absence of a reliable biomarker, analogous to the tumor markers expressed in germ cell malignancy, which had been shown to be very useful prognostic and predictive guides to treatment [10]. In the 1970s and 1980s, serum alkaline phosphatase was used as a biomarker, and while useful, suffered from the lack of specificity and sensitivity [11].

In the 1980s, T. Ming Chu and his team at Roswell Park Cancer Institute demonstrated that prostate-specific antigen (PSA), a serine protease involved in male fertility, is produced by prostatic tissues, including normal prostate, benign prostate hyperplasia and cancer, and is a marker of extent of prostate neoplasia [12]. In the ensuing years, PSA was shown to correlate, to some extent, with increasing or decreasing prostate cancer, and was incorporated into algorithms of evaluation of novel therapies [13–16]. While useful, PSA has been shown to be an imperfect marker, confounded by the presence of noncancerous prostate tissues that produce PSA and of prostate cancers that are PSA-silent, and is not sufficiently sensitive and specific to act as a sole surrogate marker of the efficacy of novel therapies.

More recently, fluxes in measured levels of circulating tumor cells have been evaluated as surrogates of utility of novel agents [17, 18], although definitive proof of reliability as a surrogate of survival remains to be established in phase III trials. To date, there is still no perfect bio-marker of advanced prostate cancer, and clinical trials continue to be confounded by heterogeneity of patterns of histology, growth rate, sensitivity to treatment, as well as the variability in patient populations entered into clinical trials.

Another potentially important issue has been the failure to recognize that a prostate cancer variant, small-cell prostate cancer (SCPC) is now widely recognized as a distinct entity, which characteristically grows and metastasizes more rapidly than classical prostate adenocarcinoma, often is associated with less hormone sensitivity and greater cytotoxic response, and a tendency to spread to soft tissue sites, such as lymph nodes, liver, and lung [19]. It is possible that some of the reported responses from the early cytotoxics that did not translate into clinically important agents for advanced prostate adenocarcinoma [20] actually represented tumor reduction in metastatic soft tissue SCPC deposits, rather than necessarily signaling activity against the classical pattern of disease.

Most experienced clinical investigators agree that this is a challenging area, and that the extant algorithms for measurement are imperfect. The attempt to address most of the issues enumerated above has led to the development of various classification systems of beneficial outcomes. The US Prostate Cancer Clinical Trials Working Group focused on the reduction of disease manifestations that are present ab initio or prevention/delay of disease manifestations that might be expected to occur [21]. While worthy and thoughtful, this influential standard operating approach really did not address the extent to which tumor flare-up and PSA release can confound evaluation (bone scans and marker levels), nor the implications of the heterogeneity of PSA response—namely, a reduction of PSA from 4 to 2 ng/ml is really not the same as a reduction from 400 to 200 ng/ml!

Similarly the European Association of Urology has struggled with this issue, and has released a series of guidelines in recent years [22, 23]. What is somewhat puzzling is the consistency of approach with the US guidelines, focusing again on the use of serial escalations of PSA (×2), but accepting serially rising PSA values of <20 ng/ml as a criterion for treatment with cytotoxics! Given the obvious discrepancy between a PSA value of <20 ng/ml and widely metastatic disease burden, and the
absence of evidence that early chemotherapy influences survival in this disease, this approach makes little sense to me. In the report from Morris et al. in this issue [24], several innovative strategies have been incorporated, including the use of a highly innovative agent based on strong preclinical data, the application of phase I/IIa design to a single category of tumor type to try to gain an early signal of utility, and the use of circulating tumor cells as a surrogate marker of response, as well as the documentation of a biological effect on a defined therapeutic target by the novel agent. The paper has now been published, and thus has achieved at least one goal of its respected team of authors; it shows that AGS-PSCA, an antibody directed against prostate stem cell antigen (PSCA) appears relatively safe for human use, has predictable pharmacokinetics and can produce steady-state blood levels, but has negligible anticancer efficacy in the doses used. Of relevance, MTD was not achieved, but rather a requisite target dose predicated on preclinical studies, and this calls into question whether the desire for haste of entry into the clinical domain led to a pragmatic dose-finding decision that yielded an undesired trials outcome. As an investment of resources, including clinician time, patient resources, and the costs of the trial, this study is a disappointment, as it neither shows a significant biological or clinical impact, nor does it seem to improve any patient-related outcome. Why was it published? It was published because the reviewers and I (as associate editor) saw merit in the thoughtful clinical design, the well-structured focus on a defined biological target, and shared the hope that it might be refined to produce a useful clinical entity with further work. That said, it is a much less pleasing phase I study than another that I approved for publication some years ago [25] from deBono and his team [26], in which abiraterone, a novel agent focused on androgen suppression after testicular inhibition, created an impressive and clinically relevant set of linked clinical and biochemical responses in castrate-resistant prostate cancer [26].

What can we learn from the differences in these two papers? We need to remind ourselves that our studies still need to focus on significant, measured patient benefit (either major objectively measured symptomatic improvement, defined and ‘real’ clinical remissions that are associated with true clinical benefit, or proven survival benefit). While the demonstration that a new drug has influenced a biochemical or molecular target may be interesting, the potential disconnect between target manipulation and clinical benefit must be underscored clearly. The use of percentage changes in outcomes (via waterfall plots, listing of PSA response percentages, and proportional changes in soft tissue or other tumor deposits) may constitute an alluring but ultimately disappointing measure of potential utility of a novel agent.

Of equal importance, when early phase trials give way to phase III, randomized trials, it will remain important to understand the heterogeneity of the constituent populations and to allow for these variations. As the sponsors of clinical trials work with increasing effort to enter cases and complete their accrual projections, it will be crucial for the clinicians leading these trials to emphasize that large accrual numbers will not simply overcome patterns of significant biological heterogeneity—thus the mixing of two distinct populations of patients, those with indolent, slowly growing metastatic prostate cancer and those with rapidly evolving, imminently lethal disease will ultimately confound analysis of phase III trials. In this latter setting, survival figures will be artificially inflated by the presence of a significant proportion of patients with indolent disease (who simply do not die, irrespective of the treatments used); however, the ability of such randomized trials to demonstrate a difference in the outcome between the standard regimen and the novel regimen may be dramatically reduced by the same population of patients with slowly evolving disease (especially when sponsors have a tendency to emphasize early reporting of outcomes).

In the past decade, progress in the management of advanced castration-resistant prostate cancer has slowed, if we define success based on improved 5- or 10-year survival, or predicated on differences in median survival that exceed a year. In an era of cost containment, it is reasonable for the community to expect more from our clinical trials, and we must be careful to consider the putative outcomes carefully before embarking on our studies. Structured clinical trials, unadorned by the window-dressing of multiple added investigations, remain our best option for progress in this complex field, but we need to focus on design considerations, the heterogeneity of potential participants, and on outcomes that will benefit the community in an obvious way. It is time to think much more carefully about the populations being recruited, rather than simple numbers of cases in the trials.

disclosures

International advisory board for Sanofi Aventis—no products mentioned in this editorial.

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Cognitive complaints in women with breast cancer: cross-cultural considerations

Research on cognitive changes following adjuvant breast cancer therapy has evolved considerably over the past decades. Earlier studies focused mainly on chemotherapy-related cognitive deficits [1], whereas more recent research has examined the potential etiological role of adjuvant endocrine therapies [2]. In most studies, cognitive function was measured with standardized neuropsychological tests [3]. If subjective cognitive complaints were assessed, various validated self-report questionnaires, ‘self-developed’ nonvalidated questionnaires, and/or semistructured interviews were used [4]. The prevalence rates of cognitive dysfunction in women with breast cancer vary between 19% and 78% [5] based on results obtained by objective testing and between 21% and 90% when self-reported [4]. This wide range may be explained by the variety of neuropsychological test or self-report measures applied, differences in designs (i.e. cross versus longitudinal), or inconsistencies in cutoffs used to classify the level of impairment. Current research focus is directed toward animal and imaging studies, to clarify the mechanisms by which chemotherapies impact brain structure, function, and consequential behavior in patients with cancer [5]. Additional results are now available on the long-term impact of chemotherapy on cognitive performance in breast cancer survivors, more than 20 years after chemotherapy, suggesting that cognitive deficits, following breast cancer diagnosis and subsequent chemotherapy, can be long lasting [6].

This emerging research on the cognitive effects of chemotherapy has coined the term ‘chemobrain’, referring to mental cloudiness or foggy thinking. Specific cognitive complaints reported by women with breast cancer cover memory lapses, troubles with concentrating, mental slowing, difficulties with decision making, and the inability to multitask. However, this term has been questioned because it does not adequately reflect the complexity of the phenomenon [7]. Besides chemotherapy, there is a range of potential confounders that can contribute to cognitive impairment, such as other treatment modalities (e.g. surgery and anesthesia or hormonal therapies), psychological factors (e.g. anxiety or depression), or cognitive reserve. Moreover, the mere awareness of potential side-effects can increase their occurrence, as suggested by a study of Schagen [8]. Cancer patients treated with chemotherapy reported more cognitive complaints and recalled fewer words on a word-learning test, after receiving information of the potential cognitive effects of chemotherapy, than those not receiving this information.

‘Chemobrain’ is also a problematic term when moving the perspective toward a non-Western culture, as highlighted by Cheung’s et al. [9] article that accompanies this editorial. In their small qualitative study, the authors aimed to gather information from multiethnic Asian (i.e. predominantly Chinese) women with breast cancer on how they experience chemotherapy-associated cognitive changes, how these changes impact their everyday lives, and how they cope to deal with...