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Prostate-specific antigen kinetics as a surrogate endpoint in clinical trials of metastatic castration-resistant prostate cancer: A review

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ABSTRACT

Prostate cancer is the most common cancer in men. Overall survival is considered the best endpoint for clinical trials, but it is difficult to use in phase-2 studies.

Although the reduction of PSA after cytotoxic chemotherapy has been identified as a valid surrogate for overall survival, it has not proven reliable for the evaluation of many biologics. Moreover, the PSA progression-free survival at 3 months was validated only for cytotoxic drugs, and the various measures of progression/delay have not been confirmed by large studies. Ultimately, outside of overall survival, no measure has been validated as a surrogate endpoint after treatment with targeted therapies and vaccine therapy.

The PSA levels have a great variability and, theoretically, the use of measures of cell kinetics and PSA may be the most reliable approach to estimate the behavior of metastatic disease. Some measures of PSA kinetics have been well developed in the clinical castration-resistant prostate cancer, the PSA doubling time and the growth rate constant. The studies about the kinetics of PSA measures are reviewed and discussed.

To date, studies that consider the measures of PSA kinetics as surrogate endpoints are still very few. However in the near future, the drug evaluation can not proceed separately, with distinct endpoints between cytotoxic and non-cytotoxic agents. Therefore, extensive analysis and validation of measures of kinetics derived from PSA, and candidates for a role for surrogate endpoint, will be needed in phase-3 studies, in order to test their effectiveness in different disease scenarios.

Introduction

Prostate cancer (PC) is the most common cancer in men and the third leading cause of cancer in the European Union.[1] While the rates of disease control are high for localized disease, 35% of patients will relapse. Initially a biochemical recurrence (BR) only occurs, which is not a surrogate for prostate cancer specific mortality (PCSM).[2] The extreme variability in the course of the PC with BR, hormone-sensitive prostate cancer (HSPC) and castration resistant prostate cancer (CRPC), requires the development of new prognostic factors for stratification of the risk of death, by defining new surrogate endpoints for overall survival (OS). A model has well described the natural history of the PC, highlighting the prognostic significance of the transition to castration resistance.[3] In fact, death occurs in the later stages of disease, mostly in metastatic CRPC (mCRPC).

Serum levels of PSA have a great variability among patients. This is explained by the fact that high-grade PC may produce less PSA per unit of tumor, and by the fact that the production of PSA is regulated by the androgen signal, thus indirectly by the androgen receptor modulators, such as hormone therapy (HT) and cytotoxic chemotherapy (CC) with docetaxel. A study of 119 surgical specimens of patients with PC undergoing radical prostatectomy (RP) made it possible to understand how important are the healthy tissue and malignancy in determining the dynamics of PSA in localized PC.[4] It follows that, in mCRPC, a similar representation of cell subpopulations could be envisaged for the remaining hormone-sensitive cells and different clones of CRPC. In particular, dominant cell clones of mCRPC would be those that dictate the kinetics of disease and PSA. The most commonly used parameters derived from the PSA in the clinic are summarized in Table 1.

The PC is a relatively slow-growing tumor, even in the case of metastatic disease. Although the OS refers to the percentage of individuals alive after a certain period of time, or period of time that elapses from the beginning of the studied treatment until death from any cause, usually the OS in metastatic cancer is very close to the cancer-specific survival, and mortality from other causes is indirectly affected by cancer itself and its treatments. From SEER survey it was found that metastatic PC has a 5-year survival of 15–31%, depending on age at onset.[5] For mCRPC the

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Table 1
PSA-related measures in mCRPC.

Static measures	
⩾30% PSA decrease	PSAD (%) ⩾30% PSA reduction from baseline Used after CC (12 weeks)
PSA progression	PSA-P (%) PSA increase above 25% of baseline Used after HT (4–8 weeks) or CC (12 weeks)
Kinetic measures	
PSA velocity	PSAV (ng/mL/year) Absolute rate of PSA changes over time Related to tumor volume and growth rate
PSA doubling time	PSADT (months) Time needed for the PSA to double Related to the exponential neoplastic growth, and independent of the baseline levels
PSA half life	PSAHL (months) Time required for the PSA to decline by one-half Related to the exponential neoplastic regression, and independent of the baseline levels
Growth rate constant	GRC (number) GRC results from an equation that takes into account regression (decay rate constant) and cell growth (growth rate constant), that occur simultaneously during cancer treatment. In mCRPC the regression portion of the curve does not predict survival, while the growing fraction does
PSA doubling time ratio	PSADT-ratio (number) It resumes the trend of PSADT after treatment (post-treatment PSADT/baseline PSADT), that after medical treatments can be prolonged (ratio > 1) or shortened (ratio 0–1)

expected probability of survival at 5 years is much lower than that of metastatic HSPC. Furthermore, the patient is older and the risk of death from other causes becomes more significant. A recent population-based Canadian study concluded that in patients with PC cardiovascular and respiratory co-morbid conditions were the most involved causes in determining the not PC-related mortality.[6]

OS is the standard reference for the evaluation of antineoplastic drugs in phase-3 studies of patients with mCRPC, but is a poor marker for phase-2 studies. As a matter of fact, to test new agents earlier in the mCRPC earlier endpoints are necessary to measure reliably the clinical benefit, thus enabling to reduce the duration of phase-2 trials. Although OS is considered the most important true endpoint, it may require very long follow-up and, in the future, will be influenced by the use of other therapies along the course of the disease, as cabazitaxel, abiraterone or sipuleucel-T.

Endpoints in clinical trials of mCRPC

To validate the effect of a surrogate endpoint (SE) of OS, the study treatment should have an effect on both the SE and OS.[7] Unlike what was originally formulated by Prentice, the simple determination of the proportion of treatment effect (PTE) is no longer recognized as a valid measure of surrogacy. Indeed, the SE should be evaluated both in terms of individual-level surrogacy, i.e. correlation between SE and OS, in terms of trial-level surrogacy, i.e. the correlation between the effects of the treatment on SE and those on OS, with two independent mathematical processes. However, the process is so complex that in medicine very few SEs were validated, so that we come to formulate a kind of hierarchy of endpoints that can better reflect the real strength of the endpoints used in different clinical situations.[8] In mCRPC it has not been reported any assessment of the trial-level surrogacy for PSA-related endpoints. An analysis of the TAX-327 study has confirmed a role for the reduction of 30% or higher serum PSA three months after initiation of chemotherapy (PSAD) and the pain response as SE in patients with mCRPC undergoing CC.[9] A similar analysis of the S9916 study confirmed a role for PSAD as SE of OS.[10]

The progression-free survival (PFS) is usually defined as the time to the first among biochemical, bone, objective progression, or death; however it is questioned as an endpoint in studies of mCRPC.[11] A pooled analysis of 1296 men with mCRPC who were enrolled in 9 CALGB trials of CC has concluded that the median OS between patients who had a progression in the first 3 months was of 9.2 months vs 17.8 months for those who had no progression during the first 3 months. In the multivariate analysis, the progression-free survival at 3 months (PFS-3 m), calculated on the measurement of PSA, predicted OS.[12] The PSA progression was the first event of progression in 60% of patients, the progression in the bone in 18%, the progression of objective measurable disease in 7%, while death was the first event in the remaining 15%. Although there is little agreement in the definition of bone progression, this is a parameter that is recovering to study; a recent analysis of 412 patients with measurable disease of TAX327 trial reported that bone progression predicted OS, with a median OS of 10.8 months in patients with bone progression compared with more than 22 months of those without it.[13]

PSAD has been identified as a valid surrogate for OS in men with mCRPC, due to the results of the retrospective analyses of two phase-3 trials with docetaxel-based regimens.[9,10] The analyses have resulted in two different PTE. This discrepancy was attributed to biological activity on the expression of PSA by estramustine, administered only in the study protocol S9916. Indeed, the reason for the discrepancy is considered unknown, especially if one takes into account the fact that prednisone is a hormonal treatment too, as well as the fact that in TAX327 study the response of the PSA was more pronounced in the weekly and less effective docetaxel arm. Even if the biochemical response has been resulted a surrogate of OS in retrospective analyses[9,10], prospective validation is still needed as well as that of the trial-level surrogacy. A major limitation of these findings is their retrospective nature, another one is in their limited application to studies of CC only. Other more recent medical studies with non-cytotoxic therapy have documented the failure of PSAD and other measures related to the serological response as SEs.

The role of PSA, PSA-related measures and other outcome measures in mCRPC was revised in 2008 by the Prostate Cancer Clinical Trials Working Group (PCWG2), which recommended to record the PSA progression at 12 weeks, reporting it as a percentage of change as compared to the baseline and maximum change at any time by using waterfall plots. PCWG2 also recommended to plan treatment for a minimum of at least 12 weeks, unless other evidence of progression.[14] Such as PSAD has not been proven reliable for the evaluation of many cytotoxic drugs, even biochemical PFS at three months (PSA-PFS-3 m) has been proven useful for cytotoxic drugs alone.[12] Outside of OS for any of the measures of progression/delay