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Platinum Priority – Editorial

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GSTP1 as a Potential Marker of Early Chemotherapy Response for Noninvasive Detection

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Approximately three decades ago, numerous researchers reported methylation of GSTP1 in different cancer types and this still seems to be of great scientific interest. We have studied GSTP1 methylation in primary tissues and bodily fluids to identify it as a biomarker for different cancer types, including prostate, bladder, and kidney [1–4]. In general, our studies identified promoter methylation of GSTP1 as a cancer-specific event and it has potential for diagnosis and monitoring of neoplastic diseases. Owing to significant advances in our understanding of the mechanisms underlying the progression of castration-resistant prostate cancer (CRPC), recent years have seen the development of novel and improved therapeutic approaches targeting this malignancy [5]. Although CRPC is a clinically heterogeneous disease with a wide array of treatment options and multiple possible sequencing combinations depending on the individual patient, docetaxel remains the mainstay of chemotherapeutic management of metastatic CRPC (mCRPC) [6]. As not all patients benefit from docetaxel, it is important to measure early response to therapy soon after the treatment has begun to quickly cease ineffective chemotherapy, minimize unwarranted toxicity, and expedite patient access to other life-prolonging therapies.

Serial measurements of serum prostate-specific antigen (PSA) levels are routinely performed to detect early PC recurrence, but PSA testing shows variable reliability as a marker of early chemotherapy response, and at least three cycles of docetaxel treatment are required before accurate clinical decisions can be made. Unfortunately, besides PSA, which has well-recognized limitations, there is a lack of reliable, noninvasive, prostate-specific predictive biomarkers of early chemotherapy response. Therefore, identification and clinical validation of novel, less expensive, noninvasive biomarker tests suitable for active surveillance and monitoring responses to mCRPC therapy are urgently needed.

Mahon et al. [7] reported that undetectable levels of circulating methylated GSTP1 DNA (mGSTP1) after one cycle of chemotherapy were associated with better overall survival (OS) and better response to therapy in patients with mCRPC, suggesting that free serum mGSTP1 may have value as an early surrogate measure of therapeutic efficacy. In this issue of *European Urology*, the same group of investigators [8] describe validation and extension of their previous observations via a post hoc analysis of a large cohort of patients form the phase 3 SYNERGY trial, which investigated the effect of custirsen in combination with docetaxel in mCRPC [9]. As addition of custirsen to docetaxel did not result in an OS benefit and had no significant effect on mGSTP1 detectability, specimens collected from patients allocated to either the study arm or the standard therapy arm of the trial were pooled, resulting in a subset of 562 patients. The study confirms that undetectable or low baseline levels of serum mGSTP1 DNA before docetaxel treatment were associated with longer OS, and reveals that addition of baseline mGSTP1 (undetectable vs detectable) to the prognostic model for the SYNERGY trial (prognostic risk groups defined according to clinicopathological variables) improves the concordance index for the prediction of OS in this group of patients. Moreover, this post hoc analysis further validates that the decrease in mGSTP1 from being detectable to undetectable at 6 wk after therapy (two cycles of docetaxel) is more highly correlated with OS than PSA

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changes at 3 mo. Furthermore, among patients whose PSA was stable or rising at 6 wk, detectable mGSTP1 remained associated with shorter OS. From these observations, they conclude that using PSA alone, chemotherapy would be continued until at least 12 wk, whereas using combined PSA and mGSTP1 data, treatment could be ceased at 6 wk if PSA was stable or rising and serum mGSTP1 remained detectable.

Although, after further validation, addition of mGSTP1 to the decision algorithm could potentially spare unnecessary toxicity for patients who fail to respond to docetaxel and facilitate decisions on early therapy adjustments, the study has several limitations that impede its immediate potential clinical utility. First, the authors' recommendation to consider ceasing docetaxel on the basis of stable or rising PSA and detectable mGSTP1 at 6 wk is based on the data from Figure 4 and Supplementary Table 4 [8]. They state that of 50 patients who eventually did not respond to treatment as they had a rising PSA at 3 mo, 34 (68%) had this combination sign at 6 wk and could have stopped treatment earlier. From the same data, the authors conclude that of 369 patients who were found to respond to treatment according to their PSA level at 3 mo, only 63 (17%) had the combination sign at 6 wk and would have stopped treatment prematurely. However, the authors did not mention that out of a total of 97 patients in the study population who had this combination sign of stable or rising PSA and detectable mGSTP1 at 6 wk, 63 (~65%) were found to benefit from treatment as measured by PSA at 3 mo. In other words, almost two-thirds of patients who would have stopped treatment at 6 wk on the basis of this combination sign would have stopped a beneficial treatment prematurely. We would assume that many patients who have already started chemotherapy would prefer to receive an additional two cycles for a ~65% chance of response. Second, out of 155 patients with PSA stable/rising at 6 wk, 116 responded (PSA TTP $>$ 3 months). Meaning that for a patient with PSA rising or stable at 6 wk, without any additional information (not using the combination sign), there is 75% of response. However, the combination sign would have indicated that treatment should be stopped for 63 of these 116 (~54%) responding patients. Third, the study focused on a CRPC population. As the authors state, docetaxel is also given in the hormone-sensitive stage as it has been proven to significantly prolong survival. One of the limitations of the study as noted by the authors is the lack of a positive experimental arm. It would be very interesting to look at mGSTP1 levels in that setting in one of the positive large phase 3 trials. This might also help to predict patients who should receive upfront docetaxel and those who should receive abiraterone, which has also been proven to prolong survival in this setting. Fourth, the study population comprises patients from both arms of the SYNERGY study. While there was no significant OS benefit with addition of custirsen, and no significant effect on mGSTP1 at 6 wk ($p = 0.2$), there might still be some direct effect of custirsen on mGSTP1. It would have been interesting to see a subset analysis for patients in the docetaxel arm only.

Unlike dynamic markers (such proteins or lipids), which may be influenced by factors unrelated to disease, and enumeration of circulating tumor cells, which requires specialized equipment and immediate processing after extraction from patients, an inexpensive, locus-specific, PCR-based circulating mGSTP1 assay may provide several technical advantages [10]. The methylated DNA marker is easily collected and stable and can be reliably detected in a small volume of frozen serum or plasma. Although this method is an attractive candidate for clinical applications because of its high sensitivity, rapid protocol, and relatively low cost, a rigorous evaluation combined with other promising PC-specific methylation markers is required to assess its potential clinical use.

Conflicts of interest: The authors have nothing to disclose.

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