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Predicting Response to Hormonal Therapy and Survival in Men with Hormone Sensitive Metastatic Prostate Cancer

Petros D. Grivas[1], **Diane M. Robins**[2], and **Maha Hussain**[1,3]

[1]Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI 48109

[2]Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI 48109-5618

[3]Department of Urology, University of Michigan, Ann Arbor, MI 48109

Abstract

Androgen deprivation is the cornerstone of the management of metastatic prostate cancer. Despite several decades of clinical experience with this therapy there are no standard predictive biomarkers for response. Although several candidate genetic, hormonal, inflammatory, biochemical, metabolic biomarkers have been suggested as potential predictors of response and outcome, none has been prospectively validated nor has proven clinical utility to date. There is significant heterogeneity in the depth and duration of hormonal response and in the natural history of advanced disease; therefore to better optimize/individualize therapy and for future development, identification of biomarkers is critical. This review summarizes the current data on the role of several candidate biomarkers that have been evaluated in the advanced/metastatic disease setting.

Keywords

prostate cancer; androgen deprivation therapy (ADT); hormonal therapy; prostate-specific antigen (PSA); prognostic biomarkers; predictive biomarkers; androgens; androgen receptor (AR)

1. Introduction

In 1941, Charles Huggins and Clarence Hodges demonstrated that castration halted the progression of prostate cancer implying that testosterone was the driver of prostate cancer cell proliferation and survival. Since then, androgen deprivation therapy (ADT) (castration) has become the cornerstone of the systemic treatment of advanced prostate cancer. Although this therapy is associated with a high antitumor effect in approximately 90% of patients, its role in advanced disease is palliative [1]. Despite 70 years of ADT, progress to date has been limited to the development of different modalities to mediate androgen deprivation, and unlike breast cancer there are no standard assays with clinical utility assessing the androgen receptor. Considering the heterogeneity in the depth and duration of hormonal response and in the natural history of advanced prostate cancer, biomarkers are clearly needed not only to

Corresponding author: Maha Hussain, Department of Internal Medicine, Division of Hematology/Oncology, 1500 E. Medical Center Drive, 7303 Cancer Center, Ann Arbor, MI 48109, Phone: +1 734-936-8906, Fax: +1 734-615-2719, mahahuss@med.umich.edu.

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better personalize therapy but also to focus and expedite new therapy development for those who are not destined to respond well to standard ADT.

Biomarkers can serve a variety of purposes. A prognostic biomarker is one that correlates with outcome, independent of treatment effects; examples include performance status, stage, Gleason's score and PSA. A predictive biomarker provides information about the probability of benefit or toxicity from a specific therapy. Examples include the expression of estrogen receptor (ER) as predictor of response to hormonal therapy in breast cancer, the mutation of KRAS as negative predictor of response to anti-EGFR therapy in colorectal cancer and NSCLC, or the V600E mutation of BRAF as predictor of response to BRAF inhibitor in melanoma.

Despite the extensive experience with prostate cancer in general and with hormone therapy in advanced stage disease, to date there are neither predictive response biomarkers to hormone therapy nor surrogate biomarkers for survival. Candidate biomarkers are often derived from retrospective multivariate analysis of clinical studies, in which such markers are correlated with outcome. It is often difficult to discern the prognostic *vs* predictive value of a biomarker, especially when there is no appropriate statistical design or a comparator control group in a clinical trial. In this review, we discuss the role and current data of several candidate predictive or prognostic biomarkers in patients with advanced/metastatic prostate cancer.

2. Potential Biomarkers of response to hormonal therapy (Table 1)

2.1. Androgens

Early studies attempted to investigate the role of hormone levels in determining response to androgen deprivation therapy. Geller et al measured dihydrotestosterone (DHT) concentration in prostatic tissue from patients with recurrent advanced prostatic cancer after estrogen therapy or castration with or without estrogen therapy [2]. A small proportion of patients had DHT level above the expected castration level. The authors suggested that patients who are castrated or treated with estrogen should have plasma testosterone and tissue DHT measurement at the time of relapse; if plasma and tissue DHT are at castrate level, further hormonal therapy would not be indicated. They also suggested adrenocortical suppression if plasma testosterone is at castrate level and tissue DHT is elevated, implying that adrenal androgen production can contribute to high tissue DHT concentration. They proposed that if testosterone is above castrate level, titration with hormonal therapy should be attempted while plasma testosterone is monitored to achieve castrate level.

The potential role of testosterone as a biomarker of response to ADT was investigated in a retrospective review of 129 patients with hormone-naïve metastatic to bone-only disease treated with 3 months of goserelin (LHRH agonist) [3]. Testosterone and PSA were measured every 3 months. Statistical analysis showed that the risk of death directly correlated with Gleason score ($p<0.01$), 6-month PSA ($p<0.01$), and 6-month serum testosterone level ($p<0.05$). The authors encouraged the achievement of optimal reduction of testosterone level with treatment.

The role of adrenal androgens has been a focus for therapy. Data from a Japanese study in castration-resistant prostate cancer patients treated with combined androgen blockade using flutamide as a second-line anti-androgen therapy Indicated that response rate and duration to flutamide was predicted by higher baseline androstenediol and lower dehydroepiandrosterone (DHEA) level, suggesting that adrenal androgen metabolites could contribute to the progression of prostate cancer [4]. Recent reports suggest that intra-prostatic/tumor concentrations of androgen hormones can be altered with ADT and might be

a surrogate marker of tumor response to anti-androgens; however, data have been inconsistent [5, 6]. A caveat regarding the utility of androgen level as predictive biomarker relates to the variability within a patient over time and the different assays by separate labs.

2.2. Androgen receptor (AR)

2.2.1. AR expression—Trachtenberg et al studied whether pre-treatment prostatic AR measurement could have predictive value in 23 patients with metastatic prostatic cancer treated with hormonal therapy [7]. Cytosolic and nuclear prostatic AR contents from pre-treatment biopsies were measured. All patients had measurable AR levels in prostatic tissue and demonstrated objective improvement with hormonal therapy. There was a strong correlation between duration of response and survival ($p<0.01$). Neither total cellular nor cytosolic AR content was associated with response; however, nuclear AR content correlated with response duration and survival ($p<0.05$). The median duration of response (7.1 *vs* 17.3 months) and median survival (14.4 *vs* 24.7 months) was significantly shorter in patients with lower compared to higher level of nuclear receptor. This was the first report of an association between nuclear AR content and hormonal response and might underline the "driving" AR transcriptional role. A study of 62 patients with untreated metastatic prostate cancer who received ADT showed that high immunohistochemical (IHC) AR content is a favorable prognostic indicator [8]. In addition, image IHC analysis of prostate cancer AR with a pattern/receptogram-oriented approach could accurately predict response to hormone therapy in patients with advanced stage, while AR heterogeneity was associated with poor prognosis in different studies [9–11].

The identification of discrete AR epitopes by color video image analysis was associated with prognosis [12]. A study using microarray-based profiling of isogenic prostate cancer xenograft models found that a modest increase in AR mRNA was the only change consistently associated with the development of resistance to anti-androgen therapy, underlining the significance of the disease setting and timing of assessment [13]. Furthermore, this study used cell models to demonstrate that increased AR level is sufficient to confer anti-androgen resistance, in part by converting antagonists to weak agonists.

Another study measured multiple biochemical variables and determined Gleason grade in prostatic biopsies obtained from 16 patients before castration or initiation of estrogen therapy [14]. Biochemical variables included 3 enzymes involved in androgen metabolism and 3 hydrolytic enzymes, AR content, tissue testosterone and DHT content. A group of 7 patients had mean response duration of 7.7 months, relapsed and died of the disease, while 9 patients had mean response duration of 18.6 months and were still responding at the time of the report. The 2 groups could not be distinguished by Gleason grade, single enzymatic activities or tissue androgen content. However, AR level was statistically different between the groups ($p<0.05$) but with considerable overlap of individual patients. The authors developed an index based on multiple enzymatic activities, which separated the groups better than any single variable alone ($p<0.02$). When salt extractable nuclear AR was included in the numerator of this index, the groups were separated almost completely, implying that the measurement of multiple biochemical variables may be a useful predictive marker.

As recently presented, PSA response to MDV3100, a novel AR inhibitor tested in patients with castration-resistant prostate cancer, was associated with unchanged or reduced AR expression ($p=0.031$). Higher baseline bone marrow and plasma testosterone level were also associated with PSA response ($p<0.05$) [15]. Studies noted above indicate that AR expression and function can change through tumor progression and may be affected by specific treatment agents with different mechanisms of action, such as the novel anti-

androgens. Therefore, the role of AR expression must be interpreted relative to the "context" of disease stage, previous and current treatment.

2.2.2. AR gene amplification—Koivisto et al suggested that hormone-refractory prostate tumors are genetically complex and show intra-tumor genetic heterogeneity [16]. Increased copy number of chromosome X and AR gene amplification may confer proliferative advantage during ADT and contribute to recurrence. They later reported that AR gene amplification was more common in prostate tumors that initially responded well to ADT, and those with response duration >12 months [17]. Tumors with earlier local relapse or no initial response did not contain AR gene amplification. The median survival after local recurrence was twice as long for tumors with AR gene amplification ($p=0.03$) as for tumors with single copy AR. However, 28% of locally recurrent tumors contained AR gene amplification compared to none of the untreated primary tumors, implying that ADT local failure may be caused by a clonal expansion of tumor cells that could continue androgen-dependent growth, despite low concentrations of serum androgens. It was concluded that AR gene amplification and wild-type over-expression may play a role in ADT failure.

2.2.3. AR gene mutations—Taplin et al reported AR mutations in 5 of 10 distant metastases from patients with ADT failure, suggesting that AR gene mutations can play a role in the metastatic progression of prostate cancer [18]. There have been data on the potential role of AR mutations in the development of androgen independence after ADT [19, 20]. Such mutations occur in distinct portions of the AR gene encoding the unstructured amino terminus (NTD), ligand-binding domain (LBD) or DNA-binding domain (DBD), and could affect ligand specificity, transcriptional activity, or mediate androgen-independent functions [21]. Mutated AR could exploit different mechanisms to evade hormonal deprivation, while many of those mutations could be selected after specific hormonal manipulation [22]. An example of mutated AR includes AR-V716M variant that creates a permissive, "promiscuous" receptor that can respond to a variety of hormone agonists and antagonists [23]. AR-E255K is another AR variant that localizes to the nucleus in the absence of androgen, promoting gene expression that could result in tumor progression [22]. AR-W435L mutation has been found in 2 patients treated with anti-androgen therapy and may promote conformational changes that impact inter-/intra-molecular interactions that influence recognition or affinity for gene response elements [22]. Some AR mutations may behave as "loss of function" in the context of development but as "gain of function" in the context of malignant transformation and treatment. AR variants can also arise from alternative splicing; their frequency increases rapidly with ADT and recedes upon hormone re-administration [24, 25]. Their role in treatment resistance may be significant since several of these AR forms are active in the absence of ligand.

2.2.4. AR polyQ tract gene polymorphisms—The N-terminal polyQ tract, encoded by a CAG repeat has been inversely correlated with AR transcriptional strength [26]. Sensitivity to Q tract length difference within a ''normal'' range (9–37 CAG repeats) is probably due to effects on overall AR structure rather than to accessory protein interactions at that site [27]. A clear association between Q tract length and prostate cancer remains controversial. However, results from genetically engineered mice support further investigation of the role that AR Q tract variation may play in late stage prostate cancer and provide a unique experimental model in which to define downstream events that may predict response to therapy [20]. For example, mice bearing tumors with a long CAG repeat (AR48Q polymorphism) fail to benefit from androgen ablation [20].

2.3. Other genetic polymorphisms

2.3.1. Luteinizing hormone-releasing hormone receptor (LHRHR), luteinizing hormone receptor (LHR), steroid hormone binding globulin (SHBG)—A recent study of patients with advanced or high-grade prostate cancer from different ethnic backgrounds reported a significant association between disease-specific survival and genetic variation in LHRHR, LHR, AR and SHBG [28]. Hazard ratios (HR) for carriers *vs* non-carriers of the LHR312 minor allele were 1.63 (95% CI 1.08–2.45) among all cases and 2.04 (95%CI 1.23–3.39) for high-grade cases. The LHRHR16 minor allele was rare in African Americans; in Caucasians (HR 1.90, 95%CI 1.15–3.13) it did not correlate with grade. The SHGB356 minor allele was associated with survival only among high-grade tumors (HR 2.38, 95%CI 1.18–4.81). It was concluded that genetic variations in the LHRHR, LHR, AR and SHGB genes were associated with outcome and merit further analysis to define their role as prognostic and predictive biomarkers; however treatment information was not provided.

The potential impact of genetic polymorphisms in LHR on the response to ADT was evaluated in 50 patients with prostate cancer [29]. Twenty-nine patients were treated for primary metastatic disease, 18 for biochemical recurrence and 12 for biochemical recurrence and radiographic metastases. In the biochemical recurrence subset, the presence of minor alleles in the LHR genotype was associated with shorter time to castration resistance; 39 months in patients with no minor alleles, 23 months in patients with 1 minor allele and 16 months in patients with 2 minor alleles ($p<0.05$). The median testosterone level during ADT was higher for patients carrying minor alleles; 7 ng/dL for patients with no minor alleles *vs* 22.5 ng/dL for patients with 1 or 2 minor alleles ($p=0.07$) with median peak testosterone level of 19 ng/dL *vs* 43 ng/dL, respectively ($p=0.01$). It was concluded that LHR genetic variation correlated with time to castration resistance and depth of castration, supporting the design of further studies to define its value as a prognostic and predictive marker.

2.3.2. Androgen biosynthesis and metabolism—Germline genetic variation in the androgen metabolic pathway was evaluated as a predictor of hormonal therapy efficacy [30]. 529 men with advanced prostate cancer treated with ADT were genotyped for 129 DNA polymorphisms of 20 genes involved in androgen metabolism. Three polymorphisms in separate genes (CYP19A1, HSD3B1, and HSD17B4) correlated with longer time to progression (TTP) during therapy ($p<0.01$), which was confirmed in multivariate analysis. Patients with >1 of these polymorphisms responded better to therapy than patients with 0–1 polymorphism ($p<0.0001$). This report suggested that genotyping of specific genetic loci might improve ADT response prediction, underlining the significance of pharmacogenomics.

Another recent study attempted to determine the predictive value of a genetic polymorphism in the testosterone transporter gene relating to ADT response duration [31]. The same group had previously shown that a polymorphism in SLCO1B3 gene increases testosterone transport into cells, and that the presence of at least 1 of the more common T allele at the 334 T>G polymorphism in this gene correlates with shorter survival. The group examined the association between this SLCO1B3 polymorphism and time to treatment resistance (androgen independence) in 68 patients with metastatic or biochemically recurrent prostate cancer. Men with the T allele tended to have shorter time to androgen independence in both patient cohorts ($p=0.11$, $p=0.18$). Combining the cohorts and stratifying by stage provided a significantly shorter time to androgen independence with the presence of the T allele ($p=0.048$). Another study suggested that the presence of the T allele is associated with rapid testosterone uptake by cells and shorter duration of response to ketoconazole, a 17 lyase inhibitor used as secondary hormonal therapy [32].

The association of germline variation in genes regulating androgen biosynthesis and metabolism pathways with response duration in prostate cancer patients receiving ADT was evaluated [33]. Overall, 747 single nucleotide polymorphisms (SNPs) from 84 genes in 304 patients with advanced prostate cancer who progressed on ADT were tested. The median patient age at ADT failure was 72 and the overall median time to ADT failure was 3.21 years. At the gene level, *TRMT11* (tRNA methyltransferase 11 homologue) exhibited the strongest association with time to ADT failure ($p<0.0008$); 2 out of 4 *TRMT11* tag SNPs were associated with time to ADT failure. The first was the intronic SNP rs1268121 (A>G) with a positive association of median time to ADT failure with the number of variant alleles ($p=0.023$): 3.1 years for 0, 4.1 years for 1, and 5.9 years for 2 variant alleles. The second was the SNP rs6900796 (A>G) in the 3' untranscribed region with a median time to ADT failure of 2.6 years for 0, 2.5 years for 1, and 3.8 years for 2 variant alleles ($p=0.023$). Four additional genes correlated significantly with ADT response (*LOC390956*, *PRMT3*, *SLC7A6OS*and *WBSCR22)*but all 4 genes had a false discovery rate >0.95.

2.3.3. Hormone response elements and genetic risk variants—The prognostic role of 49 SNPs in the estrogen response element (ERE) of particular genes was evaluated using a genome-wide database in 601 men with advanced prostate cancer treated with ADT [34]. Based on multiple hypotheses testing, BNC2 rs16934641 was found to be associated with disease progression; TACC2 rs3763763 was associated with prostate cancer-specific mortality, while ALPK1 rs2051778 and TACC2 rs3763763 were associated with all-cause mortality. The statistical significance remained in multivariate analysis with known clinicopathological prognostic factors. A combined genotype effect on all-cause mortality was observed when ALPK1 rs2051778 and TACC2 rs3763763 were analyzed in combination. Patients with a greater number of unfavorable genotypes had shorter time to all-cause mortality during ADT ($p<0.001$). This group also investigated 55 common SNPs in the genome-wide *in silico*-predicted androgen receptor elements (AREs) in the same cohort [35]. In univariate analysis, 2, 5 and 4 SNPs were associated with disease progression, prostate cancer-specific mortality, and all-cause mortality, respectively. In multivariate analysis after adjusting for known prognostic markers, ARRDC3 rs2939244, FLT1 rs9508016, and SKAP1 rs6504145 remained significant predictors for prostate cancer-specific mortality, while FBXO32 rs7830622 and FLT1 rs9508016 remained significant predictors for all-cause mortality. Strong combined genotype effects on outcome were also observed ($p<0.001$). Data have also indicated that PSA gene ARE1 −158 G/A polymorphism had no effect on PSA promoter activity *in vitro* and no association with PSA level in Japanese men; however, data suggested that ARE1 GG genotype may confer sensitivity to ADT, implying its potential value as predictive biomarker [36].

The prognostic value of 19 prostate cancer susceptibility variants in the previously described patient cohort was also investigated [37]. Two polymorphisms, rs16901979 and rs7931342, were significantly associated with prostate cancer-specific mortality ($p=0.005$, $p=0.038$, respectively), and rs16901979 was associated with all-cause mortality ($p=0.003$) after ADT. Although the effect of rs7931342 was attenuated after controlling for known clinical prognostic markers, rs16901979 remained a significant predictor of outcome after ADT ($p=0.002$). The addition of the rs16901979 status in the current clinical staging system enhanced the risk prediction of outcome particularly in the high-risk patients with distant metastasis ($p<0.017$). These results implied that incorporation of ERE, AREs and prostate cancer risk variants SNPs into predictive models might improve outcome prediction in patients with prostate cancer receiving ADT.

Germline AR-CAG repeat lengths had no significant correlation with TTP or overall survival in a group of 480 patients with recurrent or metastatic prostate cancer treated on ADT [38]. Longer AR-CAG repeat lengths (>23 *vs* ≤23) showed a non–significant trend

towards longer TTP in metastatic disease. In contrast to the genetically homogeneous mice mentioned above [20, 39], in man the AR-CAG repeat length is not, by itself, informative for response to therapy. Future studies may reveal whether it has value in concert with other markers.

2.4. TMPRSS2:ERG fusion

Genetic alterations of the androgen-regulated gene TMPRSS2 and ETS transcription factor family members ERG, ETV1, ETV4, ETV5 have been identified as a common molecular event in prostate cancer. TMPRSS2:ERG gene fusions are the dominant molecular subtype, present in almost half of prostate tumors [40]. More than 90% of ERG-over-expressing prostate cancers harbour TMPRSS2:ERG fusions [41]. ERG over-expression could contribute to androgen-independence potentially due to AR signaling disruption, while TMPRSS2:ERG expression is restored in castration-resistant setting and may contribute to progression [42, 43]. The key role of the fusion might be bypassed by androgen-independent expression of wild-type ETS factors in late-stage prostate cancer [44]. It was shown that histone deacetylase inhibitors and AR inhibitor flutamide can cause AR retention in cytoplasm, indicating androgen signalling inhibition, sustaining that this combination could be effective against TMPRSS2:ERG fusion-positive prostate cancer *in vitro* [45].

Preliminary data on the predictive value of TMPRSS2:ERG fusion has been contradictory. In one report using RT-PCR in CTC as a biomarker of sensitivity to abiraterone in 41 men with chemotherapy-treated castrate-resistant prostate cancer, TMPRSS2:ERG fusion was present in 15 patients, with a median baseline CTC of 17 [46]. PSA decline ≥50% was noted in 7 patients with and 10 patients without the fusion. TMPRSS2:ERG fusion status did not predict PSA response or other outcome. Another study also found no association between TMPRSS2:ERG fusion and outcome in prostate cancer patients primarily treated with hormone therapy, suggesting that it may not implicate hormone dependence [47]. In that study, IHC expression of protein SPINK1 was found in approximately 10% of tumors and was associated with significantly shorter progression-free survival. On the other hand, significant association between ERG gene rearrangements in CTC and the magnitude of PSA response ($p=0.007$) were reported in another study of patients with therapy-naive or castration-resistant prostate cancer treated with abiraterone [48]. In this cohort, PSA response was associated with decreased CTC and longer survival. In a cohort of 150 patients treated with radical prostatectomy, response to adjuvant ADT was associated with ERG fusion, with more significant treatment effect in ERG fusion-positive tumors [49]. Data indicated that patients treated with neo-adjuvant ADT who fail to suppress the expression of the TMPRSS2:ERG fusion have a higher risk of recurrence [50]. It is notable that a mechanistic rationale for poly-ADP-ribose polymerase (PARP) inhibition in ETS gene fusion-positive prostate cancer was recently reported [51].

2.5. Other molecular biomarkers

AR interacts in a comprehensive and dynamic manner with several co-regulators within the prostate cell microenvironment, forming an ‘AR core pathway’. A recent genomic analysis identified alterations in the components of this pathway in all examined samples from prostate cancer metastasis [52]. Dissection of the molecular interactions between AR and transcriptional co-regulators as well as neighbouring signaling pathways could identify additional mechanisms and thus candidate biomarkers of ADT resistance. For example, over-expression of 2 transcription factors, transcriptional intermediary factor 2 (TIF2) and steroid receptor co-activator 1 (SRC1) can increase AR transactivation at physiological concentrations of adrenal androgen and can provide a mechanism for ADT resistance [53]. TIF2 gene amplification and protein over-expression has been associated with prostate cancer progression [52, 54]. SRC3 (AIB1) is another important regulator of prostate cancer

proliferation, apoptosis and survival; SRC3 over-expression has been reported in prostate cancer patients [55]. Additionally, *in vitro* data indicated that up-regulation of survivin via IGF-1 signaling confers resistance to flutamide in prostate cancer cells [56]. Similarly, it was shown that over-expression of bcl-2 protects prostate cancer cells from apoptosis *in vitro* and confers resistance to androgen depletion *in vivo* [57]. A recent comprehensive review commented on the potential role of cytokines, such as interleukins; growth factors, such as Epidermal Growth Factor (EGF); intracellular kinase signaling, such as MAPK, PI3K/Akt/m-TOR, JAK/STAT, protein kinase A, and transcription factors, such as NF-kB in the development of ADT resistance [58]. It has been reported that components of the PI3K signaling pathway were genetically altered in all samples derived from prostate cancer metastasis that were examined by integrative genomic profiling [52].

At the post-genomic era, refined molecular analysis and sophisticated biochemical, genomic and proteomic platforms can contribute to the identification of novel predictive biomarkers [59]. Tumor tissue and CTC sequencing, gene expression and micro-RNA profiling techniques could reveal the potential predictive role of specific genomic, transcriptomic and micro-RNA signatures. For example, gene expression profiles of ADT-resistant tumors demonstrated that gene expression changes detected initially during ADT were no longer present suggesting reactivation of androgen and AR pathway in the absence of exogenous hormone [60]. A study using cDNA microarrays containing 1176 known genes demonstrated that 34 genes are up-regulated and 8 genes are down-regulated in androgen-independent cells [61]. Northern blot analysis did confirm the differences identified by microarrays in several candidate genes, such as c-myc, c-myc purine-binding transcription factor (PuF), macrophage migration inhibitory factor (MIF), macrophage inhibitory cytokine-1 (MIC-1), lactate dehydrogenase-A (LDH-A), guanine nucleotide-binding protein Gi, alpha-1 subunit (NBP), cyclin dependent kinase-2 (CDK-2), prostate-specific membrane antigen (PSMA), cyclin H (CCNH), 60S ribosomal protein L10 (RPL10), 60S ribosomal protein L32 (RPL32), and 40S ribosomal protein S16 (RPS16). These differentially-regulated genes correlated with human prostate cancer progression.

2.6. Novel imaging

Novel imaging modalities, such as diffusion-weighted and dynamic contrast-enhanced MRI, have also been investigated in the preclinical setting showing that the combination of early changes in several functional MRI parameters could provide additional information about therapy response and thus may help identify early non-responding patients, allowing consideration for alternative strategies [62]. Non-invasive measurement of AR signaling with a positron-emitting radiopharmaceutical targeting PSMA could be another useful tool guiding AR activity alterations during ADT [63].

3. Biomarkers of outcome (Table 2)

3.1. Prostate-specific antigen (PSA, Table 3)

The most frequently evaluated biomarker of response to hormonal therapy has been PSA level and kinetics. A multicenter Belgian study of 546 patients reported that PSA <4 ng/ml after 3 or 6 months of hormone therapy along with initial tumor grade, stage, and performance status are the most significant factors predictive of progression-free survival of hormonal treatment in patients with advanced prostatic cancer [64]. On the other hand, results from a meta-analysis, utilizing data from 3 randomized clinical trials suggested that PSA could not be statistically validated as a surrogate for overall survival; however, PSA ≤4ng/ml was a potent prognostic factor for survival [65]. This meta-analysis was criticized based on the fact that patients were not treated uniformly, PSA was not monitored in a

similar way, and it was not clear whether the same PSA assay or calibrated assays were implemented in different trials.

Baseline prognostic factors in patients with metastatic prostate cancer treated with combined androgen blockade *vs* monotherapy were explored in SWOG-8894 (a phase III trial of orchiectomy with or without flutamide) [66]. Significant baseline factors were identified, but they did not accurately predict survival of individual patients. Only 13% of patients who survived >=10 years were predicted by the model *vs* 98% of men who died within 5 years (Table 3). Data from SWOG-9346, a randomized trial of intermittent *vs* continuous hormone therapy, were used to assess whether absolute PSA after ADT is prognostic for survival in 1,345 patients with metastatic prostate cancer and a baseline PSA ≥5ng/ml [67]. After 7 months of induction ADT, 1,134 patients achieved a PSA ≤4.0 ng/ml on months 6 and 7 and were randomly assigned to continuous *vs* intermittent ADT on month 8. Men with PSA 0.2–4ng/ml had less than one third the risk of death compared to those with PSA >4ng/mL ($p<0.001$). Men with PSA ≤0.2ng/ml had less than one fifth the risk of death compared to men with PSA >4ng/mL ($p<0.001$), and significantly longer survival *vs* those with PSA 0.2–4ng/ml ($p<0.001$). The median survival was 13 months for patients with PSA >4ng/ml, 44 months for PSA 0.2–4ng/ml, and 75 months for PSA ≤0.2ng/ml. A landmark meta-analysis reported that PSA progression, defined as an increase of at least 25% than PSA level at 7 months and an absolute increase of at least 2 or 5 ng/ml, can predict survival and may be a suitable endpoint for phase II studies in the appropriate settings [68].

A few studies have associated undetectable PSA nadir with durable response to ADT [69–71]. Other studies showed that shorter time to PSA nadir after ADT initiation was associated with shorter survival, implying that a rapid initial response might indicate more aggressive disease [72, 73]. Another study associated PSA at ADT initiation with TTP in patients without metastasis; Gleason score predicted TTP in patients with metastasis [74]. PSA nadir and time to nadir were evaluated as predictors of survival in patients with bone metastasis [75]. Survival was longer in patients with lower PSA nadir. Patients with longer time to PSA nadir (>9 months) had longer survival in both lower and higher PSA nadir subgroups. A 20-year retrospective review of patients receiving primary and salvage ADT associated PSA before ADT with overall and disease-specific survival [76]. The clinical significance of PSA half-time (time for PSA to reach half of its baseline level during ADT) and doubling time after PSA nadir as predictors of response to ADT were examined in patients with metastatic disease [77]. Baseline and PSA nadir did not differ in patients with short (≤1 month) *vs* long (>1 month) PSA half-time. Patients with short PSA half-time had higher Gleason score, shorter PSA nadir duration and shorter cancer-specific survival. Patients with short (≤6 months) *vs* long (>6 months) PSA doubling time after PSA nadir did not differ in baseline PSA, PSA nadir, Gleason score and PSA half-time (Table 3).

3.2. Inflammatory markers (C-reactive protein, Interleukin-6)

It has been argued that cancer progression depends on a complex interaction between the tumor and the host inflammatory response and that the latter may have prognostic value in cancer patients. C-reactive protein (CRP) is a marker of systemic inflammatory response. It has been suggested that CRP could predict survival in patients with urological cancers, including prostate cancer, and that the incorporation of CRP into prognostic models for urological cancers improves the models' predictive accuracy [78]. The prognostic value of CRP was examined in 62 patients with metastatic prostate cancer receiving ADT [79]. On both univariate and multivariate survival analysis, CRP and PSA were significant predictors of cancer-specific survival. PSA was significantly correlated with CRP ($r(s)=0.46$, $p<0.001$). The results suggested that elevated CRP could predict poor outcome, independent of PSA, in patients with metastatic prostate cancer on ADT.

Interleukin-6 (IL-6) is a cytokine that may play a role in prostate cell regulation, prostate cancer development and progression [80, 81]. It can act as a growth signal in benign and malignant prostate cells. IL-6 and its receptors levels are increased during prostate cancer initiation and progression, and have been associated with poor prognosis [82, 83]. This is pertinent considering the cross-talk between IL-6- and AR- signaling [84]. However, differences among studies may be related to the fact that blood IL-6 levels may not reflect local concentrations in the tumor microenvironment [85]. In addition, host factors, like obesity and inflammation, may influence IL-6 levels. The predictive role of IL-6 in patients with metastatic prostate cancer on ADT has to be validated.

3.3. Metabolic markers: Body Mass Index (BMI) and bone turnover markers

A study showed that in men with androgen-dependent prostate cancer, higher BMI was associated with longer overall ($p<0.001$) and progression-free ($p=0.009$) survival, and higher likelihood to achieve PSA nadir <4ng/ml ($p=0.008$) [86]. In multivariate analysis adjusting for risk factors, higher BMI positively correlated with overall survival ($p<0.01$); overweight but not obese patients (BMI 27–29.9) had significantly better outcome *vs* normal-weight patients. A study of patients with local disease treated on ADT and irradiation correlated higher BMI independently and significantly with shorter time to PSA failure (HR 1.10, $p=0.026$) [87].

Markers of bone turnover were evaluated for their potential predictive value in patients with bone metastatic disease treated with ADT [88]. In multivariate analysis, 6-month markers of bone turnover, which were all below the baseline median level ($p=0.014$), nadir PSA <0.2ng/ml ($p=0.042$) and lower metastatic volume at baseline ($p=0.033$) were associated with longer time to skeletal-related events. Bone turnover markers below the baseline median at 6 months and PSA nadir <0.2ng/ml were associated with longer time to castration resistance ($p=0.026$, $p=0.058$, respectively). The former was weakly associated with overall survival ($p=0.092$).

3.4. Circulating tumor cells (CTC)

The clinical utility of identifying and monitoring changes in CTC and CTC molecular determinants as surrogate biomarkers of response to ADT and survival has been evaluated in large trials of novel anti-androgens in castration resistant disease [89]. The phase III trial of abiraterone *vs* placebo prospectively assessed CTC as biomarker of survival in 1,195 patients with metastatic castrate-resistant disease [90]. CTC conversion using the standard definition for unfavorable (≥5) and favorable (<5) counts predicted overall survival at 4 weeks after treatment. CTC significantly reduced the treatment effect at all post-treatment time points (HR 0.74–0.97). A reduced model with CTC and LDH was developed and suggested for further evaluation. A study recently reported that molecular CTC alterations could serve as predictive markers of sensitivity and outcome [91]. In that study, sequencing coverage and polymorphism detection thresholds in heterogeneous cell population were confirmed. In another study, initial CTC value correlated with LDH and alkaline phosphatase, but was unrelated to PSA and testosterone [92]. In multivariate analysis, baseline CTC value retained independent predictive value. The cut-point that optimized test sensitivity and specificity was 3cells/7.5ml; baseline CTC value correlated with PSA nadir benchmarks. A retrospective study demonstrated that circulating microRNA-141 in CTC could predict clinical progression and treatment response compared to other biomarkers, such as PSA and LDH, in patients with metastatic prostate cancer [93].

Despite being very promising, this approach has limitations. CTC shed from primary and metastatic tumors are admixed with blood components and are very rare, with about 1 CTC/billion blood cells in patients with advanced cancer [94]. The identity of CTC, the

mechanisms of shedding into the blood and the biological drivers of metastasis should be better characterized before using CTC as therapeutic targets and/or biomarkers. CTC isolation and characterization remain a major technological challenge; a standardized technique without inter-lab value variations is critical. In addition, it has been discussed that interaction between CTC and blood components, such as platelets, might alter the gene expression pattern of CTC, and thus their resemblance with the original tumor [95]. The prognostic/predictive value of CTC in prostate cancer has to be validated.

4. Conclusion

Several candidate biomarkers have been proposed as potential predictors of response to ADT; however, none has been prospectively validated nor has proven clinical utility to date. This is an area of unmet need and further studies are required to validate prospectively the value of genetic, epigenetic, hormonal, inflammatory, biochemical, metabolic and other molecular biomarkers in this setting. Prospective and robust validation of such biomarkers in appropriately designed and optimally executed clinical trials could result in better selection of patients who are predicted to respond to hormonal manipulation and spare the toxicity to those who are unlikely to benefit. Optimal sample storage, refined processing, quality control, and appropriate statistical designs are critical for a successful biomarker development endeavour.

Biographies

Dr. Grivas obtained his M.D. and subsequently his Ph.D. from the University of Patras School of Medicine, Greece. He completed his Internal Medicine residency at Hahnemann University Hospital/Drexel University College of Medicine in Philadelphia, US. He is currently a second year fellow in the Hematology/Oncology Program, at the University of Michigan. Dr. Grivas is a member of the American Association of Clinical Oncology (ASCO) and the American Association of Cancer Research (AACR). He is member of the Editorial Board and serves as a manuscript reviewer at several international scientific journals. Dr. Grivas is the author of over 20 peer-reviewed articles, and a book chapter in Oncology. He has given several presentations in scientific conferences, and has received several Awards and Scholarships, including an Award from European School of Oncology (ESO), and the ASCO Conquer Foundation Merit Award. His research interests include experimental and novel therapeutics in urothelial and prostate cancers, in the basic, translational and clinical trial settings.

Dr. Robins obtained her B.S. from Yale University and her Ph.D. from Stanford University, both in Biological Sciences. Following postdoctoral studies at the Columbia University Cancer Center, she became an Assistant Professor in Columbia’s Department of Biological Sciences. She subsequently joined the Department of Human Genetics at the University of Michigan, where she is currently a Professor as well as a Research Scientist in Reproductive Sciences, and the Director of Graduate Studies in Human Genetics. Dr. Robins is on several Editorial Boards, including Molecular Endocrinology and Steroids. She has been a member and Chair of numerous study sections, including those for the American Cancer Society, the NIH and the Department of Defense, and served on the ACS Council and the Board of Scientific Counselors of the National Toxicology Program. She is active in the Endocrine Society, including being the Basic Science Chair for Endo 2010 and the overall Chair for Endo 2013. She has authored more than 75 publications and several book chapters, and has given numerous named lectures and plenary addresses. Her primary research interests lie in hormonal regulation of gene expression, particularly androgen receptor action and its role in prostate cancer.

Dr. Hussain is a graduate of the Baghdad University Medical School and completed her internal medicine residency and medical oncology fellowship at Wayne State University. Dr. Hussain is a Professor of Medicine and Urology and the Associate Director for Clinical Research at the University of Michigan Comprehensive Cancer Center (UMCC) and a Co-leader of its Prostate Cancer Program. She is the Associate Chief for Clinical Research at the Division of Hematology/ Oncology, Department of Internal Medicine. Dr. Hussain is an internationally recognized clinical researcher and expert in genitourinary malignancies particularly bladder and prostate cancers. Her research is focused on novel therapeutic interventions and designs and she is funded by several peer reviewed grants. The author of over 165 scholarly articles and book chapters, Dr. Hussain has served on the editorial boards for several national and international specialty publications. Nationally, Dr. Hussain serves as the co-chair for the Prostate Cancer sub-committee of SWOG GU committee. She is a member of several federal and national scientific review panels including NCI, DOD, ASCO, and AUA. Dr. Hussain is the 2012 chair elect of the Integration Panel of US Army Medical Research and Materiel Command (USAMRMC) Prostate Cancer Research Program. She has served as chair of the Education Committee of ASCO and was the Chair for 2011 ASCO Genitourinary Cancer Symposium Program Committee. She has served as a member and the Chair for the FDA Oncology Drug Advisory Committee (ODAC).

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Table 1

Potential biomarkers of response to ADT

Serum and tissue androgens
-testosterone, dihydrotestosterone, androstenediol, dehydroepiandrosterone
Androgen receptor
-mRNA expression
-protein expression
-protein localization
-gene amplification
-gene polymorphisms(Q tract length)
-gene mutations
-splice variants
Other genetic polymorphisms
-hormones (LHRH, LH)
-receptors (LHRHR, LHR)
-enzymes (androgen biosynthesis and metabolism, estrogen biosynthesis)
-transporter and binding proteins (testosterone transporter, SHBG)
-hormone response elements (AREs, EREs)
-genetic risk (susceptibility) variants
Other molecular biomarkers
-chromosomal alterations (TPMRSS2:ERG fusion gene)
-gene expression profiling (microarrays, whole genome, exome and transcriptomic sequencing)
-proteomics (mass-spectrometry)
-micro-RNA and other non-coding RNA screening
Molecular imaging
-DW-MRI, DCE-MRI
-positron-emitting radiopharmaceuticals

Table 2

Potential predictors of survival (biomarkers of outcome)

Performance status
Co-morbidities [96]
Gleason grading score
Prostate specific antigen (PSA half-time, PSA nadir, time to PSA nadir, PSA doubling time after PSA nadir)
Inflammatory markers (C-reactive protein, IL-6)
Metabolic markers (body mass index, bone turnover markers)
Circulating tumor cells (CTC) / CTC genomic characteristics

Table 3

Studies evaluating the prognostic role of PSA along with other clinicopathological markers in men with advanced/metastatic prostate cancer treated with ADT

Ref(Year)	Number of patients	Prognostic factors (multivariate analysis)
66 (2003)	1286	minimal disease, bone pain, Gleason score, PSA
67 (2006)	1134	baseline PSA, Gleason score, performance status, bone pain
69 (2002)	153	Gleason score, PSA nadir
70 (2005)	185	PSA nadir, time to PSA nadir, bone scan findings, Gleason score
71 (2011)	650	PSA nadir, time to PSA nadir, metastatic disease, Gleason score
72 (2009)	179	time to PSA nadir, PSA nadir, Gleason score
73 (2011)	198	PSA nadir, time to PSA nadir/PSA nadir ratio
74 (2008)	553	Gleason score, metastatic disease, PSA at ADT initiation
75 (2011)	87	bone scan findings, PSA nadir, albumin, LDH
76 (2009)	548	age (diagnosis + ADT induction), stage, PSA at ADT induction
77 (2009)	131	PSA nadir, PSA half-time, PSA doubling time after PSA nadir