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Laboratory-Clinic Interface

Molecular landscape of prostate cancer: Implications for current clinical trials

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ABSTRACT

Castration-resistant prostate cancer (CRPC) is a lethal disease, and improvement with androgen-deprivation therapy has plateaued. Next-generation sequencing studies have led to significant advances in our understanding of genomic alterations in prostate cancer. The most common genomic aberrations in this malignancy are the transcription factor fusion of *TMPRSS2–ETS*, and mutations in *TP53*, *AR*, *RB1* and *PTEN*/*PIK3CA*. Some of these alterations are actionable by drugs available in the clinic. In addition, it was recently shown that aberrations in DNA repair genes, such as *BRCA2* and *ATM*, are present in both somatic and germline form in a significant minority of prostate cancer; these abnormalities can be targeted by drugs such as platinums and PARP inhibitors. In the era of tumour profiling, targeting molecular alterations may provide an opportunity for new therapeutic approaches. Although there are promising new agents to attack a variety of genomic signal abnormalities, biomarker-matched therapy (other than for androgens) have been utilised in only 2.0% of clinical trials (September 2011 through September 2014; https://clinicaltrials.gov) for prostate cancer. Enhanced efforts to define subsets of patients with prostate cancer based on their molecular anomalies, and match them with cognate therapies, warrant investigation.

Introduction

Prostate cancer continues to be the most frequently occurring cancer in men in the United States, and the second leading cause of cancer-related deaths in men [1,2]. Although the 10-year disease-specific survival rate of low-risk, localised prostate cancer patients is more than 90%, the prognosis for the 10–20% of patients who develop castration-resistant prostate cancer (CRPC) remains poor [3,4]. Therefore, novel therapeutic approaches for prostate cancer are needed.

There are 19 Food and Drug Administration (FDA)-approved agents for prostate cancer (Table 1) [5–26]. The majority of these agents ($N = 9$ (47%)) are hormonal modulators targeting the androgen pathway. Gonadotropin-releasing agonists (goserelin acetate, leuprolide acetate, histrelin acetate, or triptorelin pamoate), and androgen-receptor blockers (flutamide, and bicalutamide) were approved by the FDA before 2000, and have been the backbone of prostate cancer treatment [5–11]. However, advanced prostate cancer ultimately develops resistance to androgen-deprivation therapy. Newer agents, such as abiraterone and enzalutamide, are effective in CRPC [16]. Abiraterone inhibits CYP17, a critical enzyme in the synthesis of testosterone, and therefore decreases androgen synthesis in adrenal glands, testes, and tumour cells [12,13]. Enzalutamide is a newer androgen-receptor (AR) blocker, which has greater affinity for the receptor, and it inhibits the nuclear translocation of the AR, DNA binding, and co-activator [15]. Although abiraterone and enzalutamide showed survival benefit in castrate-resistant disease, prostate cancer cells eventually develop resistance [13–15]. Therefore, androgen deprivation alone is not sufficient to control prostate cancer.

Phase III studies demonstrate survival benefits with chemotherapeutic agents (docetaxel and cabazitaxel) and improved quality of life (mitoxantrone) [16–19]. However, their effectiveness is not long lasting, and toxicity eventually becomes a challenge in the prostate cancer patient population. Sipuleucel-T, a novel cancer vaccine, was associated with prolonged overall survival compared to that seen in a sham-treated control [25,26].

Bone-seeking radiopharmaceuticals use unique properties of specific radioisotopes to target metastatic disease in the bone. Strontium-89 and samarium-153 are beta particle emitters, and they are effective in relieving bone-related symptoms; they do not, however, improve survival [20,24]. Radium-223 was the first

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Table 1
FDA-approved agents for prostate cancer [5–26].

Class	Name	Year of FDA approval	Mechanism of action	Refs.
Hormonal agents	Goserelin acetate	1989	GnRH agonist	[5]
	Leuprolide acetate	1989	GnRH agonist	[6]
	Histrelin acetate	1991	GnRH agonist	[7]
	Bicalutamide	1995	Androgen receptor blocker	[8]
	Flutamide	1989	Androgen receptor blocker	[9]
	Triptorelin pamoate	2000	GnRH agonist	[10]
	Degarelix	2008	GnRH antagonist	[11]
	Abiraterone	2011	CYP17 inhibitor	[12,13]
	Enzalutamide	2012	Androgen receptor blocker	[14,15]
Chemotherapy	Estramustine	1981	Microtubules inhibitor	[16]
	Mitoxantrone	1996	Alkylating agent and TOPOII inhibitor	[17]
	Docetaxel	2004	Microtubules inhibitor	[17,18]
	Cabazitaxel	2010	Microtubules inhibitor	[17,19]
Bone-seeking radiopharmaceuticals	Strontium-89	1993	Beta particle emitter	[12,20]
	Samarium-153	1997	Beta particle emitter	[12,24]
	Radium 223	2013	Alpha particle emitter	[21,22]
Bone-directed agents	Zoledronic acid	2002	Osteoclast inhibition	[16,23]
	Denosumab	2013	RANK ligand inhibitor	[16,23]
Immunotherapy	Sipuleucel-T	2010	Cancer vaccine	[25,26]

Abbreviations: GnRH = gonadotropin-releasing hormone; RANK = receptor activator of nuclear factor kappa-B.

bone-seeking radioisotope that showed an overall survival benefit [21,22]. Other bone-directed agents, zoledronic acid and denosumab, attenuated skeletal-related events [23].

Taken together, most of the progress in the past decade in prostate cancer treatment has been made possible by the development of newer androgen pathway-targeted therapy. As mentioned, nine therapies that manipulate androgen levels have been approved for prostate cancer (Table 1). These treatments are not without side effects, including hot flashes, fatigue, sexual dysfunction, and osteoporosis [27]. Although there are well-known genomic alternations in prostate cancer, molecular-targeted therapy for this malignancy has not been extensively studied in the clinic. We review the genomic landscape of prostate cancer and implications for clinical research in this disease.

Genomic aberrations in prostate cancer

Prostate cancer shows biological heterogeneity, which likely reflects underlying genomic diversity. The oncogenic landscape of prostate cancer has become clearer after next-generation sequencing and microarray-based interrogation [28–33]. Common genomic aberrations in prostate cancer include: transcription factor fusion of *TMPRSS2–ETS*, and mutations and copy number alterations of *TP53*, *AR*, *RB1* and *PTEN*/*PIK3CA*, as well as alterations in DNA repair genes such as *BRCA2* and *ATM* (Table 2) [33–55].

TMPRSS2–ETS fusion

Transmembrane protease, serine 2 (TMPRSS2) is a serine protease regulated by androgens [34–36,56]. *ERG* and *ETV1* belong to the ETS transcription factor family, and are fused with *TMPRSS2* in approximately 50–79% cases of prostate cancer [28–32,36]. *TMPRSS2–ETS* fusion is associated with a poor prognosis in localised prostate cancer [57]. Recent preclinical studies have identified targetable cofactors, such as PARP1, DNAPK, and HDAC1, and inhibition of these cofactors has conferred preferential sensitivity in ETS-positive malignancies in preclinical models [37,38,58]. A number of phase I studies of PARP1, DNAPK, or HDAC1 inhibitors have been done in patient populations including those with *ERG* fusion-positive malignancies [38]. Ongoing phase II studies have focused on the inhibition of PARP1 as a strategy to target *ETS* fusion-positive disease, including a randomized study with veliparib, in which patients with prostate cancer are stratified based on the fusion status of *ETS* (NCT01576172) [38]. Other PARP1 inhibitors being assessed as monotherapy in CRPC include olaparib (AZD-2281/KU-0059436; phase II, clinicaltrials.gov identifier NCT01682772) and niraparib (MK-4827; phase I expansion cohort in prostate cancer, NCT00749502) [38].

TP53

Approximately 3–47% of prostate cancer specimens harbour *TP53* mutations, and 2–15% contain homozygous deletion [28–31,33]. The tumour suppressor p53 plays a key role in maintaining genomic stability and preventing tumourigenesis [59]. A previous study demonstrated that the $TP53^{R270H}$ mutation was sufficient to induce prostate cancer in mice [60]. Mutation or deletion of *TP53* was associated with increased risk of recurrence [61]. *Wee*-1 inhibitors, such as MK-1775, can target *TP53* mutated malignancy [62]. The *TP53* gene also regulates the expression of VEGF, and anti-angiogenic agents, such as bevacizumab, were associated with improved survival in patients harbouring *TP53*-mutant tumours, in a retrospective study [41,63,64]. A phase III randomized trial comparing docetaxel/prednisone with or without bevacizumab in CRPC patients found no difference in overall survival [65]. However, this study did not screen patients based on the *TP53* mutation, and their *TP53* mutation status was not investigated.

Androgen receptor (AR)

From 2–18% of prostate cancer specimens harbour androgen receptor (*AR*) mutations, and 5–52% demonstrate amplification [28–31,33]. Amplification occurs rarely in untreated primary prostate cancers, with the observed frequency between 0% and 5% [66,67,69,70]. However, amplification of the *AR* was found in 20–52% of hormone-refractory prostate cancers [28–31,66–71]. The *AR* belongs to the steroid hormone group of nuclear receptors and acts as a ligand-dependent transcription factor that controls the expression of specific genes. Prostate cancer initially responds to androgen-deprivation therapy, but it eventually becomes castration-resistant. The *AR* remains a key regulator in CRPC [42]. There are several proposed mechanisms of resistance. An AR