Prostate Cancer

VAL 201 – An Inhibitor of Androgen Receptor-associated Src and a Potential Treatment of Castration-resistant Prostate Cancer

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Abstract
Prostate cancer is the second leading cause of cancer death in men in the US. The initial treatment of metastatic prostate cancer is androgen deprivation (castration) therapy and this is achieved through either surgical or medical castration, however these therapies are also associated with undesirable side effects including impotence, tumour flare and loss of bone mass. Over time, nearly all patients with metastatic disease become resistant to androgen deprivation, progressing to castration-resistant prostate cancer (CRPC), and at this stage of the disease the prognosis is extremely poor (<50 % survival at two years). Currently there are few treatment options for CRPC. Only four have been found to extend survival and none are curative. Effective treatment of CRPC is a major unmet clinical need, and the identification of alternative therapeutic targets is an active focus of research. In this article we discuss the development of a new agent, Val 201 as a potential future treatment for CRPC. VAL 201 targets the association of androgen receptor with Src, a non-receptor tyrosine kinase signal-transduction protein that is important in tumour cell proliferation, and represents a novel and exciting approach for cancer chemotherapy.

Keywords
Castration-resistant prostate cancer, androgen receptor, VAL 201, Src, tumour cell proliferation

Development of Castration-resistant Prostate Cancer
There are multiple mechanisms that can drive disease progression to CRPC, and most involve the AR pathway. Resistance to castration therapy can be due to altered AR sensitivity, amplification of AR or mutations. Alternative splicing of the AR gene can lead to the expression of ARs lacking the ligand-binding domain and which are constitutively active. Additionally, CRPC can be caused by ectopic androgen synthesis, such as androgen synthesis by the adrenal glands, the tumour itself or increased conversion of extra-gonadal androgens to testosterone. Other mechanisms of progression to CRPC include modulation of AR co-regulators (again leading to increased signalling of the AR pathway) and, lastly, there can be activation of compensatory AR-independent pathways, which lead to cell proliferation and inhibition of apoptosis.

Current Treatments for Castration-resistant Prostate Cancer
Prior to 2010 docetaxel was the only approved agent for CRPC, and currently only three other systemic agents have demonstrated an increase in overall survival in patients with metastatic CRPC. Mitoxantrone, a type II topoisomerase inhibitor, has not demonstrated a survival improvement but remains a palliative therapeutic option.
Currently, docetaxel plus prednisone every three weeks is the preferred first-line treatment for CRPC. Docetaxel is a well-established anti-mitotic chemotherapy agent and in the TAX 327 Phase III clinical trial was shown to confer an overall survival advantage of three months, when compared to mitoxantrone.24-25 A study by the Southwest Oncology Group showed a similar survival benefit.26

In April 2010, the FDA approved the use of the immunotherapy sipuleucel-T for men with less advanced disease. Treatment with sipuleucel-T is only recommended for patients with a good performance level, and not those with symptomatic, rapidly progressive or visceral disease. Sipuleucel-T is an autologous cancer vaccine, produced by exposing the patient’s antigen-presenting cells (APCs) to a recombinant fusion protein (PA2024), after first being collected from the patient’s white blood cell fraction.27 PA2024 is a prostate antigen, prostatic acid phosphatase, fused to granulocyte macrophage colony-stimulating factor (an activator of immune cells). The activated APCs are then re-infused back into the patient. In a Phase III clinical trial the sipuleucel-T treatment arm was shown to extend the mean survival by 4.1 months as compared with placebo.28

Cabazitaxel (plus prednisone) also gained approval by the FDA in 2010 as a therapeutic option for patients who have previously failed docetaxel-based chemotherapy.29 Cabazitaxel is a semi-synthetic taxane derivative with antimitotic activity. Approval was based on the results of a Phase III trial comparing cabazitaxel with mitoxantrone, with a 2.4-months improvement in overall survival seen in the cabazitaxel treatment arm (HR 0.72, p<0.0001).30 Treatment caused a high rate of grade 3-4 neutropenia, that was observed in 81.7 % of patients in the cabazitaxel treatment arm.

In 2011, the FDA approved the use of abiraterone acetate plus prednisone for patients with metastatic CRPC who have previously been treated with docetaxel. Abiraterone is an androgen synthesis inhibitor, and selectively and irreversibly inhibits both the 17α-hydroxylase and the C17,20-lyase function of the enzyme cytochrome P450 c17.13 This is a key enzyme required for the synthesis of testosterone/dihydrotestosterone from weak adrenal androgens.14 A Phase III, randomised, placebo-controlled clinical trial demonstrated a statistically significant improvement in overall survival in patients treated with abiraterone (14.8 months versus 10.9 months in the placebo arm).31

Castration-resistant prostate cancer is now the second most common cause of male cancer-related mortality in the US.3 Castration therapy, in addition to abolishing the receptor-dependent signalling pathways, also inhibits the receptor’s transcriptional action which affects positive actions of androgens such as neuroprotection and bone preservation. In principle, new therapies could be developed that are more specific, abolishing receptor-dependent signalling but preserving AR transcriptional action.

**Overview of the Mechanism of Action of VAL 201**

In human mammary and prostate cancer cells, steroid hormones or epidermal growth factor (EGF) trigger association of the AR-estriadiol
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Figure 1: Inhibitory Mode of Action of VAL 201 on Tumour Cells – The AR-derived VAL 201 interferes with Steroid and EGF Signalling

A = Androgen; AR = Androgen Receptor; E2 = Estradiol; EGFR = Epidermal Growth Factor Receptor; ER = Estradiol Receptor; Erks = Extracellular Signal Regulated Kinases. PTK = Protein Tyrosine Kinase; SH2 = Src Homology-2 Domain; SH3 = Src Homology-3 Domain; Sox = Sox of Sevenless; Ss = Src Homology-2 Domain Containing.

Cell cycle progression pathway

Figure 2: Inhibition of Xenograft Development in VAL 201 (S1) Treated Mice versus Scrambled Peptide (Ss) and Vehicle

A clear suppression of tumour growth is seen over a four-week treatment period. The proliferation status of cancer cells was determined by Ki67 positivity, which was significantly decreased (p=0.005) in LNCaP tumours treated with VAL 201.

As noted earlier, hormone therapies are associated with undesirable side effects including impotence, hot flashes, gynaecomastia, increase in body fat, osteoporosis, decrease in muscle mass, depression and fatigue. These side effects can significantly affect quality of life. The current first-line chemotherapeutic treatment for CRPC is docetaxel which is a cell cycle specific agent, and thus cytotoxic to all dividing cells in the body. Because of this, side effects such as alopecia and neutropenia are common. Owing to the mechanism of action of VAL 201, this peptide is potentially less toxic than other first choice therapeutic options for prostate cancer. Additionally this peptide is being developed into an oral formation and has a good pharmacokinetic profile in vivo.

To further evaluate VAL 201 as a therapeutic option for the treatment of prostate cancer, the following clinical studies have been proposed. Firstly, a microdosing study is being considered so that at an early stage of clinical development good human pharmacokinetic data will become available. However, the option to dose pre-prostatectomy patients is being contemplated, and this would give access to biopsy samples for subsequent targeting analysis. The clinical development programme of VAL 201 is currently at the planning stage.

Future Developments

VAL 201 is equally efficacious in androgen-AR and estradiol-ER modulation, and this opens up a range of potential disease targets beyond prostate cancer. There is significant potential for the use of

Preclinical Studies

As previously mentioned, VAL 201 has been shown to be highly effective against prostate and breast cancer cell lines and mouse xenografts. The in vitro half-life for VAL 201 in human liver microsomes was 49 minutes, classified as intermediate metabolic clearance, and in human plasma the half-life of the peptide was 95 minutes (personal communication with Dr George Morris). An oral formulation of VAL 201 peptide targets AR/Src association and prevents ER/AR/Src association. In the absence of VAL 201, the ER/AR/Src complex activates Sos (an exchange factor for Ras GTPase). Sos induces activation of Ras and the Ras-dependent kinase cascade including Erks, which leads to cell cycle progression.

In mammary and prostate cancer cells androgen or estradiol induce association of ER/AR complex with Src, which activates Src and affects the G1 to S cell cycle progression (see Figure 1). VAL 201 inhibits this interaction, and the subsequent activation of the AR or ER, inhibiting steroid- and EGF-dependent DNA synthesis. Most importantly, inhibition of Src by VAL 201 takes place after androgen binding, and allows inhibition of growth but does not block desirable receptor-dependent transcriptional activity. This difference should eliminate the majority of side effects that are associated with androgen therapies. VAL 201 works by mimicking the amino-acid sequence responsible for human AR interaction with Src, and has been demonstrated to suppress tumour growth in tissue culture and the growth of LNCaP prostate cell xenografts in nude mice. VAL 201 does not inhibit the S phase entry and cytoskeletal changes in AR-negative prostate cancer cell lines induced by EGF or serum treatment.

The Src protein has three major domains: SH2, SH3, and the PTK catalytic domain.
VAL 201 as a treatment for other metastatic cancers including breast, endometrial and ovarian cancer, but its development for these indications is at an early stage. Preclinical testing, has demonstrated that VAL 201 inhibits the estradiol-induced association between the ER and Src without interfering in receptor-dependent transducing activity in MCF-7 mammary cancer cells.25

Another potential role for VAL 201 in the future is an alternative to surgical or chemical castration in patients with low-risk prostate cancers. Upon diagnosis of low-risk early stage prostate cancer, an ‘active surveillance’ approach is currently adopted due to the risk/benefit considerations of available drugs. Active surveillance refers to a strategy of forgoing immediate treatment after a diagnosis of prostate cancer in favour of regularly scheduled testing and clinical examinations to monitor disease progression. Many patients are unhappy about a perceived lack of treatment after being diagnosed with cancer and forgo active surveillance, opting for surgical or chemical therapies with undesirable side effects. The theoretically favourable safety profile of VAL 201 means that it could potentially be prescribed at this stage to delay disease progression. Because VAL 201 is a novel therapy, there is the potential for combinational activity with other anti-cancer agents. Synergy of the Src inhibitor dasatinib has been demonstrated in non-prostate-cancer models for cisplastin, doxorubicin and temozolomide, and therefore there is potential for VAL 201 to demonstrate combinational activity.

The median survival for patients with metastatic castration-resistant prostate cancer with the recommended available treatments is approximately 18 months, and there is an urgent unmet need for more effective therapies. VAL 201 is the first example of a specific inhibitor of steroid-receptor-dependent signal transducing activity and this represents a novel and excelling approach for cancer chemotherapy. It has the potential to become an important and effective treatment option for patients with CRPC and may also facilitate therapeutic intervention at the early stages of prostate cancer. The clinical development of this drug will be watched with great interest by the entire oncology community and patients alike.