Advances in Advanced Prostate Cancer Therapies – A Review by a Patient-Scientist

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Methods/Design
A review of recent literature was conducted to evaluate the potential of approved therapies (in the USA) on advanced prostate cancer. A historical search was made of earlier developments as well to determine how they have influenced current thinking and advances.

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Roadmap:

Background

I. Androgen axis

II. Immunotherapy

III. Attack cancer directly
One in 6 men will ultimately be diagnosed with prostate cancer.

Of these men, one in six will die of Prostate cancer.

Spreads to pelvic bed lymph nodes

Watershed event --- Distant metastases

90% of distant metastases to bone.
Others to lymph nodes, and soft tissue.
I. The Androgen axis

Androgens: Testosterone and dihydrotestosterone (DHT)

Protein, Androgen receptor (AR)

1. Androgen binds to the AR.
2. AR+androgen translocates into nucleus.
3. ARs pair up (dimers) and bind to DNA.
How the androgen receptor works.

1. Androgen binds to the AR.
2. AR+androgen translocates into nucleus.
3. ARs pair up (dimers) and bind to DNA.

Genes expressed within PCa cell. Causes cell to grow and reproduce.

Androgen axis therapies: Stop Androgen Production (androgen deprivation therapy), or Stop 1 (Enzalutamide), or Stop 2, or Stop 3 (Bromodomain inhibitors).

Androgen Deprivation Therapy (First line therapy used today)
Remove androgens (primarily testosterone). This can extend survival by many years.

Discoverer: Charles Huggins 1941. Almost 75 years ago. Charles Huggins received the Nobel Prize in Physiology/Medicine in 1966 “for his discoveries concerning hormonal treatment of prostatic cancer.”

“the importance of this discovery (androgen deprivation) far transcends its practical implications; for it means that thought and endeavor in cancer research have been misdirected in consequence of the belief that tumor cells are anarchic.” Payton Rous
The work of Huggins showed us what some of the rules of Prostate Cancer are.

Studies on prostatic cancer, I. The effect of castration, estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate, C Huggins and CV Hodges, Cancer Research 1, 293-297 (1941).
ADT: Chemical reduction of testosterone by agonist (Leuprolide) or an antagonist (Degarelix) of Gonadotropin Releasing Hormone (GnRH, also known as LHRH). GnRH works on the pituitary via the hypothalamus to inhibit testosterone production in the testes.

ADT in advanced prostate cancer. Results of the CS21 trial showing the probability of progression free survival vs. time upon taking Degarelix or Leuprolide as a the first line ADT. After 1 year (vertical dashed line) those on Leuprolide could change to Degarelix, and the curve shows the result of those changing. After B Tombal et al., European Urology 57, 836-842 (2010).
Castrate resistant prostate cancer

Enzalutamide (MDV3100, Xtandi): Stop [1], the binding of Androgen to the AR. Fill the AR binding pocket.
Abiraterone Acetate (Zytiga)

Abiraterone inhibits the production of Androgen from Cholesterol

Cholesterol $\rightarrow$ Androgen

**What does Abiraterone do?**

Abiraterone inhibits an enzyme, CYP17A1, that acts on precursor steroids before they become androgens. These two enzymatic functions are hydroxylase and lyase activity.

Just in time therapy

Experimental: Bromodomain inhibitors JQ1 binds to DNA and blocks the androgen receptor from binding.

II Immunotherapy strategies:
1. Vaccines or 2. Checkpoint Inhibitors or 3. Both

Therapeutic Vaccines most often “boost” Dendritic Cells

Dendritic cells: Cells that digest foreign (cancerous) antigens and display them on MHC complexes on their surface to activate T-cells.

*Ralph Steinman created a revolution in immunology when he discovered a beautiful cell by just looking through a microscope. .... He showed that dendritic cells are critical for initiating the most important immune responses.*

Michel C Nussenzweig, Nobel Prize lecture 2011.
Sipuleucel-T (FDA) approved.

Therapeutic vaccine.

Patient’s Dendritic cells exposed to antigen (in laboratory) then reinfused into patient.

Antigen (generic, not from patient) = Prostatic Acid Phosphatase (PAP) + granulocyte-macrophage colony stimulating factor (GM-CSF) from recombinant fusion gene. Should be given early, but not FDA approved until castrate resistance. Cost -- $120,000

Survival curve vs. time on Sip-T and placebo. The median survival time occurs at 50% probability. (After PW Kantoff et al., New England Journal of Medicine 365, 411-422 (2010).)

Notes:
1. Extend Overall survival 4.1 months.
2. No effect for 6 months.
Immunotherapy takes time to work. Start early.
### Some other Vaccine Therapies

<table>
<thead>
<tr>
<th>Vaccine Therapy</th>
<th>Active agent</th>
<th>Tumor associated antigen</th>
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<tbody>
<tr>
<td>Prostvac</td>
<td>Engineered viruses</td>
<td>PSA antigen.</td>
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<tr>
<td>DCVAC</td>
<td>Patient’s dendritic cells activate T-cells.</td>
<td>Antigens within whole LNCaP cells.</td>
</tr>
<tr>
<td>Others (DCVax, GVAX, BPX-201)</td>
<td>Patient’s dendritic cells activate T-cells.</td>
<td>LNCaP cells, PSMA, PSMA.</td>
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Prostvac vaccine
Virus containing engineered genes.

Prime + boost using two vital agents.

The design and action of Prostvac.  

(A) The design of a Prostvac virus. A recombinant DNA molecule containing the genes for PSA+TRICOM genes inserted into a DNA plasmid (circular piece of DNA). This is then inserted into the virus particle.  

(B) The virus infects cells of the patient and upon cell death the infected cell releases antigens of the virus (PSA and TRICOM).  

(C) Antigen presenting cells (APCs) take in the antigens and present them on their surface. This activates T cells to attack cancer cells that express PSA. (More details at CG Drake, Nature Reviews of Immunology 10(8), 580-593 (2010).)

TRICOM = TRIad of COstimulatory Molecules = B7.1 + ICAM-1 + LFA-3 Molecules to encourage T-cell response.
Immune Checkpoint Inhibitors

CTLA-4, PD-1  Not much progress in Prostate Cancer
$100,000 – $150,000

... suspending the brakes. Not so much harnessing the immune system, but unleashing it to attack whatever it was going to attack. Jim Allison (on CTLA-4 checkpoint inhibitors)

How CTLA-4 inhibition works. (Left panel) A dendritic cell with a cancer antigen presented on its MHC binds to the T cell receptor (TCR) of the T cell. A second signal is needed to fully activate the T cell, and that is the binding of a CD80 or CD86 to a CD28 on the T cell. (Center Panel) The second signal causes the T-cell to express CTLA-4. But CTLA-4 binds better to CD80 or 86 than CD28, thus shutting down further activation. (Right Panel) An antibody (CTLA-4 inhibitor) binds to CTLA-4 so that CD80/26 can again bind to CD20 to fully activate the T-cell so that it is hungry to attack tumors. (See e.g. A Vasaturo et al., Frontiers in Immunology 4(417), 1-14 (2013).)
Engineered T-cells

A great idea that almost no one is pursuing for prostate cancer. Idea is to modify a patient’s T-cells so that they attack prostate cancer cells. The modification is a chimeric antigen receptor built to bind to antigens on Prostate Cancer cells.

A comparison of normal T-cell activation with that of T-cell attack of cancer cells using chimeric antigen receptors, CARS. (A) The natural activation of T-cells by binding of the T-cell receptor to an antigen presented on the MHC of an antigen presenting cell (APC). The activated T-cell has to then reproduce and hunt for the tumor cell. (B) A first generation CAR that by itself is capable of producing Signal 1. Signal 2 requires binding to an APC. (C) A 2nd generation CAR that has co-stimulatory proteins in the CAR that alone presents both Signal 1 and Signal 2. Adding proteins to the CAR creates 3rd generations that produce Signal 3 as well. (B&C) Note that the tumor cell is directly involved in engineered CAR T-cells, in contrast to the natural process (A). (More details at DW Lee et al., Clinical Cancer Research 18, 2780-2790 (2012).)

Phase IB trial redesign to test role of IL2 with anti-PSMA designer T-cells to yield responses in advanced prostate cancer, RP Junghans, Journal of Clinical Oncology 30, 2012 (suppl 5; abstr 70, American Society of Clinical Oncology annual meeting); Role for IL2 adjunctive cotherapy for suppression of a solid tumor with designer T-cells: Phase I trial data in prostate cancer, RP Junghans, Journal of Clinical Oncology 31, 2013 (suppl 6; abstr 216, American Society of Clinical Oncology annual meeting).
III. Direct targeting to kill cancer cells:
Chemotherapy, radiation, Ra1223

Chemotherapy

Taxanes: Docetaxel FDA approved 2004 for metastatic PCa.

Original source the Yew Plant.

Has benefit in about ½ of patients. Serious side effects.

<table>
<thead>
<tr>
<th>Major chem drugs</th>
<th>Description</th>
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<tr>
<td>Taxane</td>
<td>A generic name for a class of anticancer chemotherapy agents.</td>
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<tr>
<td>Docetaxel (Taxotere)</td>
<td>A first line chemotherapy drug for prostate cancer. Acts on microtubules during cell division.</td>
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<tr>
<td>Paclitaxel (Taxol)</td>
<td>The first taxane to be discovered.</td>
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<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>An early chemotherapy drug (not a taxane). Acts on DNA topoisomerase during cell division.</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>A platinum-based drug used for aggressive prostate cancer variants. Glues-up DNA to trigger cell death.</td>
</tr>
<tr>
<td>Etoposide</td>
<td>A drug sometimes used with Cisplatin that acts on DNA topoisomerase during cell division.</td>
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How taxanes work.

Microtubules change length by growing and retracting. Taxanes interfere with microtubule dynamics especially during mitosis (cell division). Taxanes affect all dividing cells, not just cancer cells and cause hair to fall out etc.

Microtubule – Helical structure of two proteins -- alpha and beta tubulin. Growth and retraction occurs at the ends and gives microtubules “push and pull” power.

Cell division. Mitotic spindle consisting of microtubules anchored to centrosomes and tugging on chromosomes to separate them during the process of the cell dividing into two. This spectacular image illustrates that life is surely magical. Courtesy National Heart, Lung, and Blood Institute, National Institutes of Health, Nasser Rusan.
Big news about early application of Docetaxel.

Apply early to patients with high tumor burden – early means as soon as Androgen Deprivation Therapy is initiated. Christopher Sweeney. Announced at ASCO meeting in Chicago, May-June 2014.

A comparison of overall survival for those patients with high tumor burden.

Taxanes lose their effectiveness -- Chemo Resistance

Popular explanations include:
1. Change in tubulin isotypes (not all tubulin is the same).
2. Efflux mechanisms (removal of taxanes).
3. Alteration of cell death pathways.
4. Mutations of tubulin that affect the polymerization and dynamics of microtubules.
**Einstein Goes After Prostate Cancer**

Positrons travel faster than light (in tissue) and emit Cherenkov radiation. Use FDG to produce positrons which then produce UV/Blue Cherenkov radiation that activates decorated nanoparticles of TiO2 to produce antioxidants that attack cancer.

FDG $\rightarrow$ UV-Blue light $\rightarrow$ Excites nTiO$_2$-Tf-Tc $\rightarrow$ Toxins $\rightarrow$ Kills Cancer.

Summary

- Great opportunities for advancement.
- Genomics still plays a minor role (outside the laboratory).
- Modern improvements have been incremental.
- Our understanding has greatly improved, but advances in therapies are modest.
- Immunology holds promise, but so far has not delivered significantly to the treatment of advanced prostate cancer.
- The 1941 work (Huggins) still provides more benefit to prostate cancer patients than any of the modern developments.

Patients don’t turn down the modern improvements. A starving man will eat what is available.

General Reference:
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