

ASCO 2009
Update on new therapies for
Castration-Resistant Prostate
Cancer (CRPC)

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Issues to cover

- Changes in how we assess response
- Prevention updates
- Screening updates
- New options for CRPC patients including chemotherapy, biologics, and vaccines

Assessing efficacy

- Measure PSA as a waterfall chart
- Assess measuring soft tissue lesions that are 2 cm or larger
- Avoid looking at the overall response rate
- Assess time to event (duration of a treatment working)

Prevention & Screening for Prostate Cancer

- 25% of cancer cases incidence in US men are prostate cancers
- 1 in 6 men will be diagnosed with prostate cancer
- Only half men in the US are being screened
- 9% of cancer deaths are from prostate
- Risk of death from prostate cancer is more in AA men compared to other races

Two options

- Detect the disease early so it can be cured
- Prevent the disease.

Prevention

- SELECT trial was negative: Vitamin E and Selenium are not protective agents
- PCPT: Finasteride versus Placebo: Decrease the risk by 25% but increases high-grade cancers when they occur

Prevention

- REDUCE trial
- Men with elevated PSA (<10) and negative biopsy
- Placebo versus Desaturide 0.5 mg daily
- Biopsies at 2 and 4 years
- 8000 men randomized
- 23% reduction in positive biopsies on the treatment arms

Prevention

What can we conclude in 2009?

- Low fat diet
- Exercise
- Vitamin E and Selenium do NOT work
- Other dietary changes are not proven
- 5-alpha reductase inhibitors seem to be effective

Screening

- Recent recommendations from

USPTF

NCCN

ACS

Screening USPTF

- Inadequate evidence to show that screening in men younger than 75 improves clinical outcomes as opposed to treatment at time of clinical detection
- In men over 75, there was adequate evidence to show that screening has small to almost no benefit

Screening ACS & NCCN

Annual DRE and PSA starting at age 50, but frank discussion between patients and physicians to make an informed decision is important (ACS)

NCCN is usually pro-screening but recommends against screening in patients who have less than 10 years of life expectancy

Why talk about screening?

- Currently, 58% of US men are screened
- Currently, 1 in 6 men will be diagnosed
- If 100% of men are screened, we would detect cancer in 1 out of 3 men

New Therapies

Abiraterone Acetate (AA)

Study # 1

- AA is a major inhibitor to CYP17 a major enzyme in androgen biosynthesis
- Phase II study in chemo-naïve patients
- AA given at 1000 mg daily with prednisone 5 mg twice daily
- 33 pts enrolled, 27 evaluable
- >90% decrease in PSA occurred in 41%
- Median time to PSA progression has not been reached

Abiraterone Acetate (AA)

- Well tolerated
- HTN in 6%
- Edema in 15%
- Hypokalemia in 12%
- 19% experienced improvement in their performance status and their function

Abiraterone Acetate (AA)

Study # 2

- Phase II in Taxotere failure patients
- 1000 mg daily in 47 patients
- Steroids at low doses were allowed
- 15% had > 90% PSA decline
- 17% had reduction in tumor measurement
- HTN, edema, and hypokalemia were the most observed adverse events

Abiraterone Acetate (AA)

Study # 3

- 58 patients with CRPC, who failed Taxotere
- 1000 mg daily
- 32 patients never received ketoconazole
- 45% had > 50% PSA decline
- Median time to PSA progression in keto-naïve patients were 198 days
- AA is being studied in phase III trials

Ixabepilone+Mitoxantrone+Prednisone

- Phase II study in pts who failed Taxotere
- 37 evaluable patients
- 38% (14 pts) had >50% PSA decline
- 15 pts had measurable visceral disease, 2 of which had objective response
- 2 pts had pneumonia, 3 pts had significant fatigue, 1 pt had myocardial infarction.
- In general, well-tolerated.

Sagopilone

- Sagopilone is the first fully synthetic epithelone with in-vitro activity in human cancers including prostate cancer
- Phase II study where patients received the drug IV over 3 hours every 3 weeks with prednisone
- No prior chemotherapy was allowed
- 42% had > 50% PSA decline
- 29% of 35 pts had reduction in tumor size
- Main side effects: neuropathy and fatigue

Anti-IL6

- Elevated serum IL-6 is associated with prostate cancer progression, PSA elevation, and poor prognosis.
- CNTO-328 is a chimeric anti-IL6 monoclonal antibody
- CNTO-328 was combined with Taxotere in CRPC
- CNTO-328 was given 6mg/kg every 2 weeks (then increased dose) with standard 3-week Taxotere

Anti-IL6

- 59% of patients showed PSA responses
- Actual measurable tumor responses were seen in 17 patients
- CNTO-328 was safely combined with Taxotere and a phase II study is being done using the dose of 12 mg/kg of CNTO-328

AT-101

- Direct and indirect inhibitor of Bcl-2 family protein
- Bcl-2 is important protein in cancer cell growth and prevention of apoptosis
- Phase II study combining AT-101 (40 mg twice daily 1-3) with Taxtere and Prednisone
- 36 chemo-naïve and 40 patients with prior chemotherapy
- 67% with > 50% PSA decline in the chemo-naïve cohort

AT-101

- In the chemo-refractory patients, 22% had > PSA decline
- Oral drug that clearly has activity in CRPC and can be combined with Taxtere
- Majority of adverse events were grade 1 and 2

MDV3100

- Second generation anti-androgen
- Engineered for activity in prostate cancer cells that over-express the AR
- Binds the AR better than Casodex
- Induces cell kill (apoptosis) in prostate ca
- In vitro, MDV was effective in cells that were resistant to Casodex

MDV3100

- Phase I/II to determine safety and anti-tumor activity
- No more than 2 prior chemotherapies (one with taxotere) were allowed
- 140 pts with 78% having bone disease
- Well-tolerated (fatigue and nausea)
- MTD was 240 mg daily (seizures were noted at higher doses)

MDV3100

- 62% of chemo-naïve pts had > 50% PSA decline
- 51% of chemo-failure pts had > 50% PSA decline
- 36% of chemo-naïve pts had soft tissue disease response
- 12% of chemo-failure pts had soft tissue response

MDV3100

- Pre-chemo: time to PSA progression, not reached
- Post-chemo: time to PSA progression, 189 days
- With this treatment, CTCs were less in some patients
- **AFFIRM** trial: MDV versus placebo in taxotere-failures looking at survival

OGX-011

- Clusterin is over-expressed in prostate cancer and correlates with higher Gleason
- OGX-011 (Custirsen) decreases clusterin in tissues and can be safely combined with chemotherapy
- 80 pts randomized to receive OGX with taxotere/pred or taxotere/pred alone
- Looking at responses and PSA responses

OGX-011

- Treatment was well-tolerated with only lymphopenia more common with OGX
- Rigors and fevers occurred with the OGX loading dose
- >50% decline occurred in 58% (with OGX) and 54% (without) of pts
- PFS (7.2 versus 6.4 months)
- OS (23.8 versus 16.8 months) P=0.06

PROSTVAC-VF-Tricom

- Randomization between vaccine and placebo in asymptomatic or minimally symptomatic pts with CRPC
- 125 pts from 43 sites
- Gleason 7 or less
- No prior chemotherapy
- No narcotics for tumor-pain were allowed
- Liver, brain, or lung mets pts were excluded

PROSTVAC-VF-Tricom

- 7 vaccinations over 5 months
- Days 0, 14, 28, 56, 84, 112, 140
- Progression assessed at 2, 4, and 6 months
- No difference in PFS
- Improvement in OS with vaccine (P=0.006), 8.5 months difference

IMPACT AUA 2009

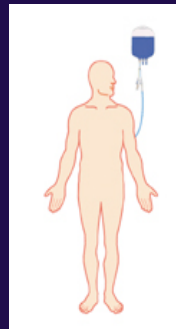
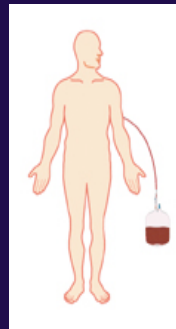
- 512 pts, chemo-naïve, asymptomatic
- Provenge versus placebo (2:1)
- OS: 25.8 months versus 21.7 (P=0.03)
- Provenge is given 3 times, 2 weeks apart, and then no treatment
- Well-tolerated with only infusion-related side effects
- No impact on PSA but an impact on OS

Provenge Administration

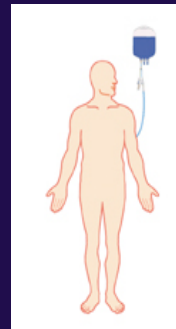
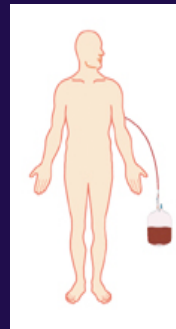
3 Leukaphereses, 3 Infusions

- Three doses prepared from the patient's own cells
- Cells for each dose collected by leukapheresis
- Each dose administered via a single intravenous infusion at Weeks 0, 2, and 4.

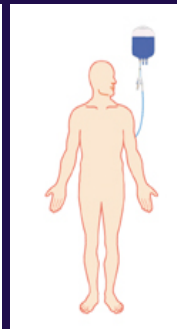
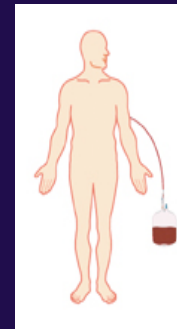
Infused
at Weeks



0



2



4

Immunotherapy

- Not clear why there is an impact on OS while no significant impact on PFS or PSA

Revlimid + Taxotere

- Phase I established the ability of combining revlimid with taxotere
- A current registration phase III trial is open to compare taxotere/prednisone versus taxotere/prednisone and revlimid

Available Trials at OSSC

- Chemotherapy Naïve patients:

Revlimid single agent (25 mg oral daily for 21 days followed by 7 days of rest)

Torisel single agent IV weekly infusion

Tarceva oral therapy (closed, to be published in J Urology 8/2009)

Available Trials at OSSC

- Chemotherapy patients:

Taxotere versus taxotere and revlimid

Available Trials at OSSC

- Chemotherapy failure patients:

Phase II trial of adding Sorafenib oral therapy to the last chemotherapy given

Phase I/II trial combining Sorafenib and Gleevec therapy (both oral agents)

Available Trials at OSSC

- Chemotherapy Responsive patients:

GM-CSF SQ injections for 14 days
followed by 14 days of rest.

Summary

- There is a change in how we assess response to chemotherapy
- No clear understanding as to what is the best surrogate marker when using biologic therapies for CRPC
- Many treatment options are on the way including targeted agents and immunotherapy