

Updates on Prostate Cancer

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Disclosure

- **Barry R. Goldspiel, PharmD, has no real or apparent conflicts of interest to report**

Learning Objectives

- Describe the current standard of care for a patient with advanced prostate cancer
- Discuss potential treatment options for a patient with advanced prostate cancer who has failed initial therapy
- Explain the biologic rationale for studying vaccines in prostate cancer patients
- Formulate a treatment and monitoring plan to prevent metabolic complications in a patient with prostate cancer receiving androgen deprivation therapy

Updates on Prostate Cancer: Outline

- Overview of current management
 - Review NCCN Guidelines
 - Current issues with therapy for localized disease
 - Current issues with therapy for advanced disease
 - Review of androgen deprivation therapy
 - Complications of androgen deprivation therapy

Updates on Prostate Cancer: Outline

- Therapy for relapsed advanced disease
 - Overview of standard chemotherapy
 - Update on docetaxel + prednisone
 - Overview of second-line chemotherapy
- Overview of new agents in clinical trials
 - Clinical trial endpoints
 - New agents
- Conclusions

NCCN Guidelines: Prostate Cancer V.1.2008 – Localized Disease

NCCN Guidelines: Prostate Cancer V.1.2008 – Localized Disease

NCCN Guidelines: Prostate Cancer V.1.2008 – Locally Advanced Disease

Localized Therapy

AHRQ Research Review

- No one therapy can be considered preferred
 - Treatment should be individualized
 - All treatment options result in adverse effects
 - More randomized controlled trials needed

Localized Therapy

AHRQ Research Review

- Adjuvant androgen deprivation therapy
 - When bicalutamide combined with radical prostatectomy, radiation therapy, or watchful waiting
 - No reduction in mortality or recurrence
 - Did not reduce progression

Localized Therapy

Quality of Life

- 1201 patients and 625 spouses/partners
- Rx = prostatectomy, brachytherapy, or external beam radiation therapy
- Expanded Prostate Cancer Index Composite (EPIC-26)
- Service Satisfaction Scale for Cancer Care (SCA)

Localized Therapy

Quality of Life

Significant Reduction in Quality of Life

Domain	Treatment	P value
Sexuality	Radiotherapy	<0.001
Urinary Incontinence	Brachytherapy	<0.001
Urinary Obstruction	Radiotherapy	0.009
	Brachytherapy	<0.001
Bowel Function		
Vitality or Hormonal Function	Radiotherapy	<0.001
	Brachytherapy	<0.001

Prior Androgen Deprivation Therapy (ADT)

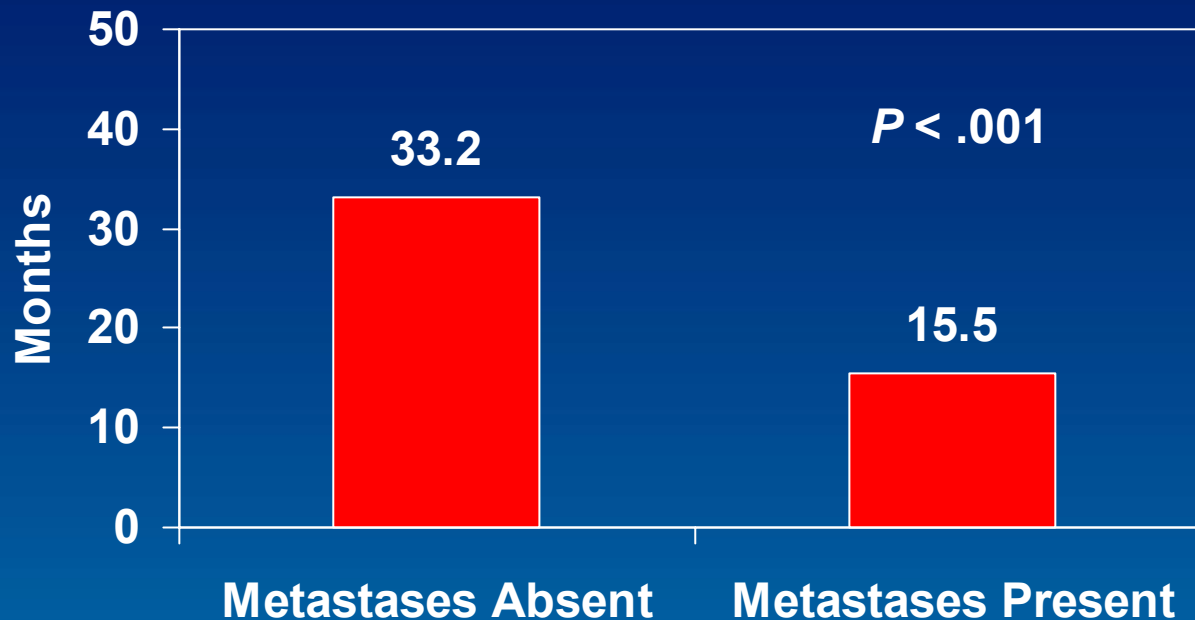
- 553 patients (51% M-, 49% M+)
- Efficacy of ADT related to:
 - Absence of metastases
 - Lower Gleason score (M + only)
 - Lower PSA at ADT initiation (M – only)
 - ADT as part of local treatment (M -/M+)
 - Shortened time to progression (TTP)
 - [HR = 1.45, 95% CI 1.10 -1.91]

PSA = prostate-specific antigen; HR = hazard ratio; CI = confidence interval.

Ross RW, et al. *Cancer*. 2008;112:1247-53.

Prior Androgen Deprivation Therapy

Median Time to Progression



NCCN Guidelines: Prostate Cancer V.1.2008 – Advanced Disease

NCCN Guidelines: Prostate Cancer V.1.2008 – Advanced Disease

2006 ASCO Practice Guidelines Update

- Standard initial options
 - Bilateral orchiectomy or LHRH agonists
- Antiandrogens effective?
 - Nonsteroidal antiandrogens – possibly
 - Steroidal antiandrogens – no
- Combined androgen blockade
 - Can be considered
 - (NCCN Guidelines: Precede or co-administer with LHRH agonist and continue for at least 7 days in patients with overt metastases or at risk for flare)

ASCO = American Society of Clinical Oncology; LHRH = luteinizing hormone-releasing hormone.

Loblaw DA, et al. *J Clin Oncol*. 2007;25:1596-605.

2006 ASCO Practice Guidelines Update

- Early or deferred therapy
 - Early ADT
 - 17% decrease in relative risk [0.83 (0.74-0.94)] for prostate cancer specific mortality
 - No decrease in overall mortality [0.98 (0.95-1.01)]
- Intermittent ADT
 - Insufficient data – need clinical trials

Benefits of Androgen Deprivation Therapy

Advanced Disease

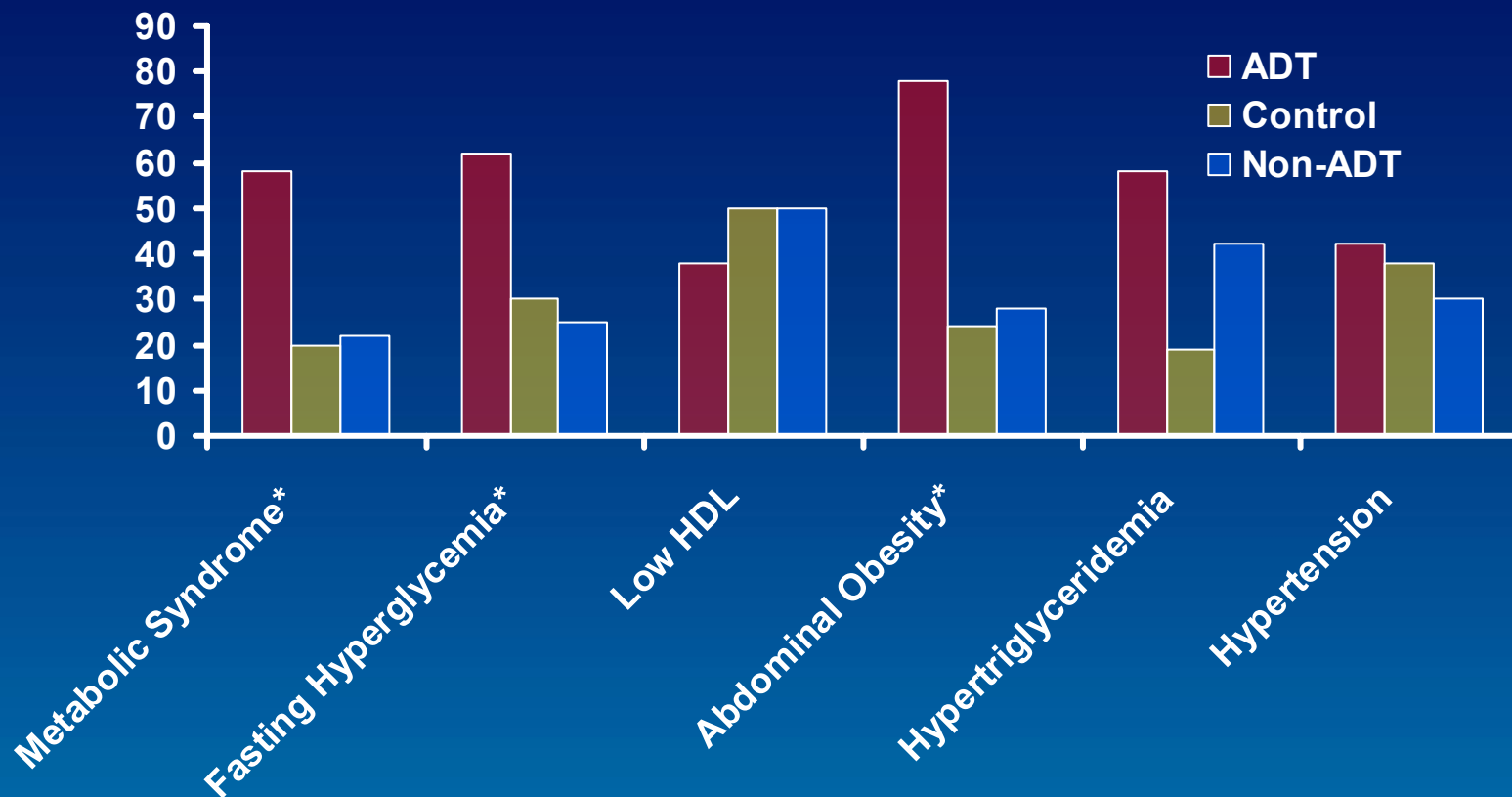
Decrease in	Control 95% CI	ADT 95% CI	P value
Cord compression	4.9	1.9	<0.025
Ureteral obstruction	11.8	7.0	<0.025
Metastases	11.8	7.9	<0.05
Pathologic fracture	7.9	2.3	NS

Complications of Androgen Deprivation Therapy

- Metabolic syndrome
- Bone loss

Complications of ADT

Metabolic Syndrome



* = statistically significant.

Metabolic Syndrome Monitoring/Management

- If ADT planned for >1 year
- Monitor
 - Blood pressure
 - Glucose
 - Weight

Complications of ADT

Bone Loss

- Annual bone mineral density loss of up to 4.6%
- Most significant loss within 1 year
- Annual rates similar for LHRH agonist (-2.1% to -4.6%) and LHRH agonist + antiandrogen (-0.6% to -4.5%)
- Increased fracture rate for ADT
 - Orchiectomy: 7-year incidence of 13.6% vs 1.1%
 - Claims data: RR 1.21 (1.09 – 1.34)
 - 25,000 patients: RR 1.37 (1.2 – 1.57)

Complications of ADT

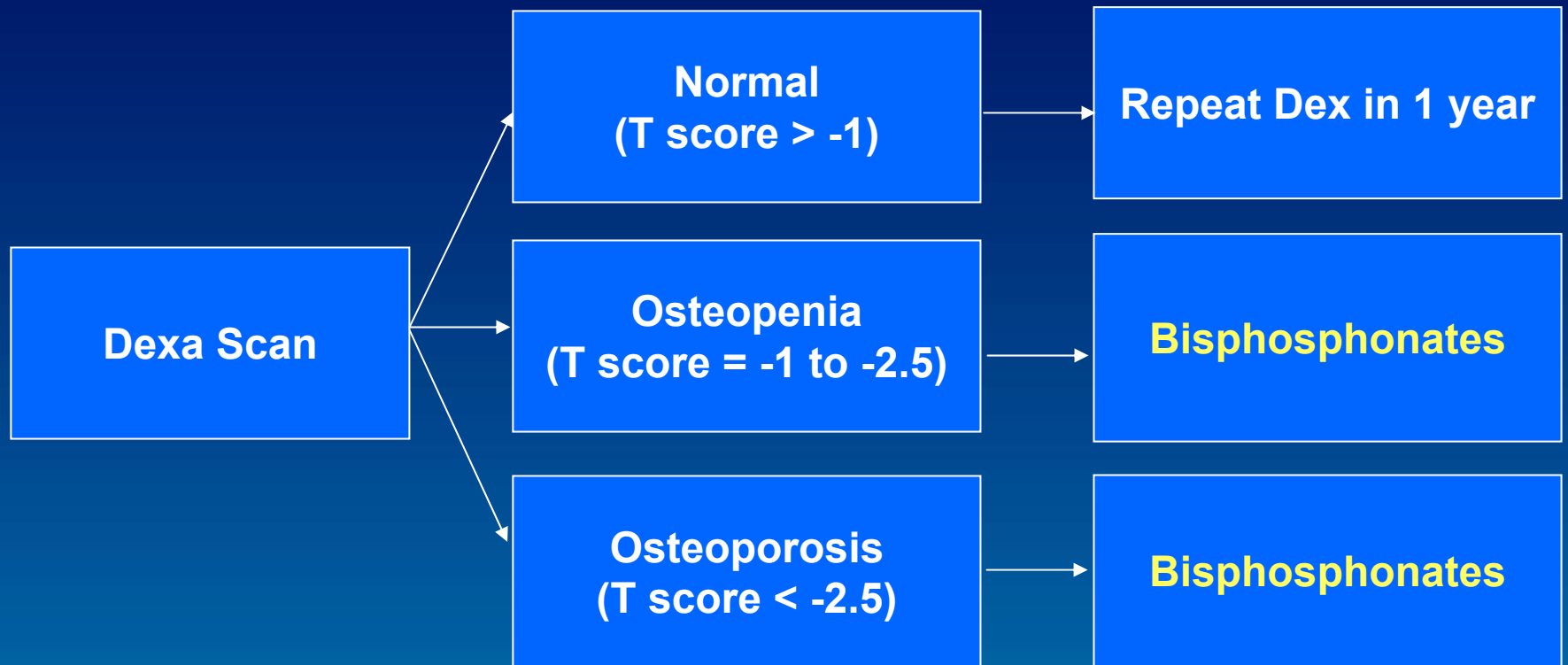
Bone Loss

- Risk factors for men on ADT
 - White race
 - Body mass index <25 kg/m²
 - ADT duration

Bone Loss With ADT: Prevention

- Dietary supplementation
 - Calcium 1200 to 1500 mg/day
 - Vitamin D 400 to 600 IU/day
- General measures
 - Exercise
 - Increase dairy
 - Increase sun exposure
 - Smoking cessation

Bone Loss With ADT: Management



Bone Loss With ADT: Management

- Bisphosphonates
 - Zoledronic acid 4 mg IV
 - Once or every 3 months for up to 1 year
 - Alendronate 70 mg orally weekly
 - Pamidronate?
 - Monitor for osteonecrosis of the jaw
- Selective estrogen receptor modulators (SERMs)
 - Raloxifene
 - Toremifene
- Estrogen

Therapy for Relapsed Advanced Disease

■ NCCN Guidelines

- Participate in clinical trial
- Docetaxel-based regimens are standard of care for first-line treatment
- Every 3 weeks docetaxel + prednisone
 - Alternatives
 - Every 3 weeks docetaxel + estramustine
 - Weekly docetaxel + prednisone
 - Every 3 weeks mitoxantrone + prednisone

Cancer Care Ontario Practice (CCOP) Guideline

- CCOP Guideline for non-hormonal therapy in men with castration-resistant prostate cancer
 - Clinical or chemical evidence of progression – docetaxel 75 mg/m² IV q3 weeks with prednisone 5 mg twice daily
 - Survival advantage + palliation
 - Alternative therapies
 - Weekly docetaxel + prednisone
 - Mitoxantrone + prednisone (or hydrocortisone)
 - No survival advantage, but may palliate

Cancer Care Ontario Practice (CCOP) Guideline

■ CCOP Guideline statements

- Docetaxel-based chemotherapy is only treatment that confers survival advantage
- Timing should be discussed
- Continued on ADT
- Symptom control should be optimized
- Use of estramustine-based regimens not recommended

ASCO Endorsement of Cancer Care Ontario Practice (CCOP) Guideline

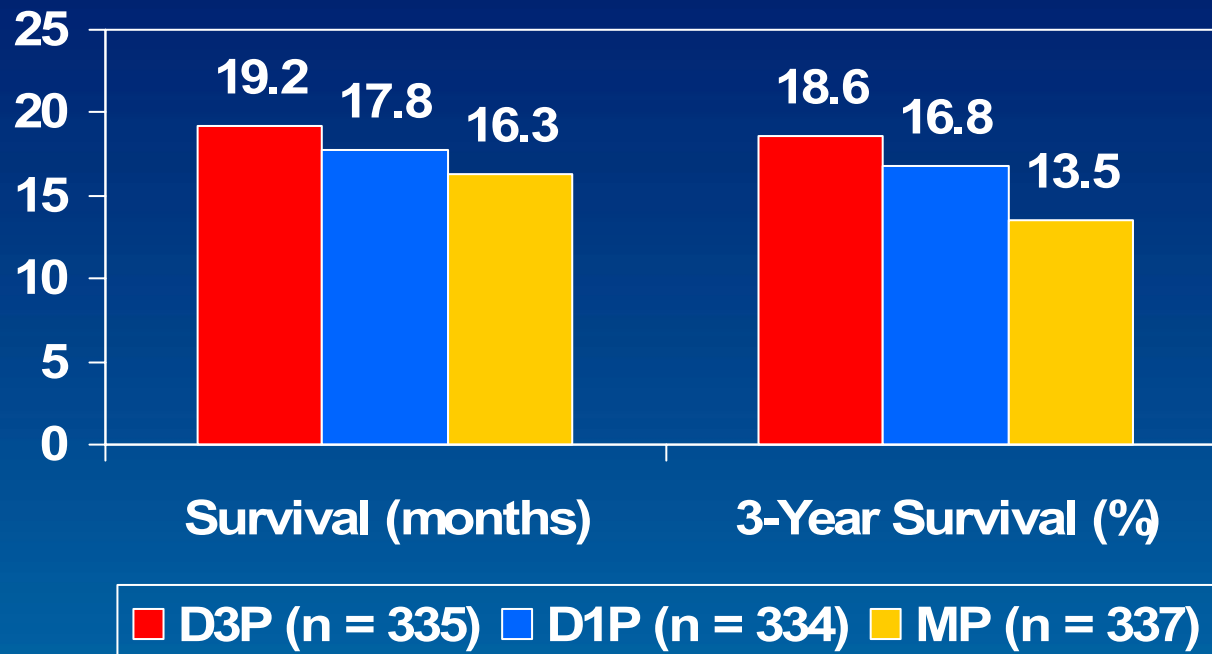
- ASCO Board of Directors approved a policy to endorse guidelines developed by other organizations
- Rigour of Development subscale of AGREE
- CCOP Guideline scored high (86%) for methodological quality
- Endorsed the Guideline
 - Two reviewers noted importance of considering other non-hormonal therapies and that CCOP has other guidelines published on radiopharmaceuticals and bisphosphonates

Docetaxel-Based Regimens

- SWOG 9916
 - Docetaxel + estramustine (17 mos) vs mitoxantrone + prednisone (15.6 mos) [$P = .01$]
- TAX 327
 - Docetaxel weekly vs docetaxel every 3 weeks (19.2 mos) vs mitoxantrone + prednisone (16.3 mos) [$P = .009$]

TAX 327 Update

Survival Time



Hazard Ratios for Survival Time

D3P: 0.79 (0.67-0.93)
[*P* = .004]

D1P: 0.87 (0.74-1.02)
[*P* = .086]

Second-Line Therapies

- Alkylating agents
- Anthracyclines
- Antimetabolites
- Camptothecins
- Epothilones
- Vaccines
- Angiogenesis inhibitors
- EGFR inhibitors
- Camptothecins
- Epothilones
- Taxanes
- Platinums
- Vinca alkaloids
- Combinations of the above

Clinical Trial Endpoints – Progressive Prostate Cancer and Castrate Levels of Testosterone

- Controlling, relieving, or eliminating disease manifestations
- Preventing or delaying disease manifestations expected to occur
- Prostate cancer progressing despite castrate levels of testosterone are **CASTRATE RESISTANT** not hormone-refractory

Clinical Trial Endpoints – Progressive Prostate Cancer and Castrate Levels of Testosterone

Variable	Criteria
PSA	Control/relieve/eliminate: % change Progression: >25% increase and >2 ng/mL
Soft-tissue	Control/relieve/eliminate: RECIST with caveats; assess lymph nodes \geq 2cm Progression: RECIST with caveats
Bone	Control/relieve/eliminate: New or no lesions Progression: \geq 2 lesions
Symptoms	Independent of other outcomes Pain and analgesia Quality of life

Alternative to Monitor Therapy?

- CellSearch™ system
- Counts circulating tumor cells (CTC) in blood
- FDA approved for metastatic breast cancer, colorectal cancer, and prostate cancer (2/08)
- 65 centers, 231 patients
- Decrease associated with response to therapy
- <5 CTC better survival than >5 CTC
- Independent predictor of progression-free and overall survival
- CTC + PSA

FDA = Food and Drug Administration.

Vogelzang N. Proc AACR 2008.

Second-Line Therapies

- Satraplatin
- Angiogenesis inhibitors
 - Thalidomide
 - Bevacizumab
 - Sorafenib
- Targeting HER2
 - Pertuzumab
- Immunotherapy
 - Vaccines
 - Sipuleucel-T
 - GVAX

HER2 = human epidermal growth factor receptor 2.

Satraplatin

- Third-generation oral platinum
- More lipophilic and stable
- First-line therapy
 - Phase 2 – CA142-013
 - Phase 3 – CA142-029
 - Phase 3 – EORTC 30972
- Second-line therapy
 - Phase 2 – CA142-026
 - Phase 3 – SPARC

Satraplatin: First-Line Therapy

Trial Name	Agent(s)	N	Response
CA142-013	Satraplatin 100 mg/m ²	39	26% PR 16.7 mos MS
EORTC 30972	Satraplatin 100 mg/m ² + prednisone vs prednisone	50 of 380	33.3% PR 14.9 mos MS
CA142-029	Satraplatin 100 mg/m ² + prednisone vs prednisone	14	Terminated early

Satraplatin: Second-Line Therapy

Trial Name	Agent(s)	N	Response
CA142-026	Satraplatin 100 mg/m ² + prednisone	10	Terminated early
SPARC (Phase 3)	Satraplatin 80 mg/m ² + prednisone vs prednisone	950	RR 0.6 (0.5–0.7) Increased progression- free survival PSA response: 25.4% vs 12.4% (<i>P</i> < .01)

Satraplatin – Adverse Effects

- Reversible myelosuppression
 - Neutropenia
 - Thrombocytopenia
- Nausea/vomiting (13% Grade 3/4)
- Combination with prednisolone
 - Diarrhea
 - Hyperglycemia
 - Cardiovascular

Thalidomide

- Phase 2 study in 63 patients using low-dose (200 mg, n = 50) vs high-dose (1200 mg, n = 13)
- 18% PSA response in low-dose arm
- Phase 2 study in 75 patients: docetaxel q1 week (n = 25) to thalidomide 200 mg + docetaxel (n = 50)
- Results favored combination
 - 53% vs 37% PSA response
 - Median survival: 25.9 mos vs 14.7 mos ($P = .0407$)
 - Thrombotic events in 12/43 patients (LMW heparin)

LMW = low molecular weight.

Figg W, et al. *Clin Cancer Res.* 2001;7:1888-93; Figg W, et al. *J Clin Oncol.* 2005;23:2113-4.

Bevacizumab

- No response as single agent
- Phase 2 trial using bevacizumab + docetaxel + estramustine (n = 17)
 - 9/17 partial responses, 81% >50% PSA decline
- Phase 2 trial using bevacizumab + docetaxel + thalidomide (n = 39 evaluable)
 - 17 (59%) partial responses, 87% >50% PSA decline
 - Significant toxicities: febrile neutropenia, syncope, colon perforation, bleeding, thrombosis

Bevacizumab

- Bevacizumab + docetaxel in docetaxel-pretreated patients
- 20 patients treated with bevacizumab 10 mg/kg + docetaxel 60 mg/m² every 3 weeks
- 3 (37.5%) partial responses, 55% >50% PSA decline
- Well tolerated

Sorafenib

- Vascular endothelial growth factor (VEGF) important in prostate cancer
 - Progression from early to advanced disease
 - Step in metastasis
- Ras/Raf/MAP kinase/ERK pathway is dysregulated in castrate-resistant prostate cancer
- Sorafenib inhibits VEGF and Raf

Sorafenib

- Single-arm phase 2
- Sorafenib 400 mg orally twice daily
- 22 patients with median PSA of 53.3 ng/mL
- No complete or partial responses
- 7 patients progression-free by PSA at 7 months
- Median progression-free survival was 1.8 months
- 6 patients with PSA progression had a PSA decline after drug discontinuation
- 2 patients showed bone scan improvement
- Typical sorafenib adverse effects

HER2 and Prostate Cancer

- HER2 overexpressed in some prostate cancers
- No activity for trastuzumab, gefitinib, or erlotinib
- Pertuzumab
 - Different epitope than trastuzumab
 - Binds to HER2 dimerization domain

Pertuzumab and Prostate Cancer Chemotherapy-Naïve Patients

- 68 patients treated at either 420 mg or 1050 mg
- No declines in PSA >50%
- Adverse effects
 - Diarrhea and other gastrointestinal disorders
 - Fatigue
 - LVEF decrease
 - Hemolytic-uremic syndrome

Pertuzumab and Prostate Cancer Progression After Taxanes

- 41 patients received 840 mg loading dose followed by 420 mg
- No complete or partial responses or >50% PSA decline
- Of 30 patients: 5 had stable disease
- Retrospective survival analysis – prolonged survival at 12 months:
 - Pertuzumab [0.74 (0.58 – 0.85)]
 - Historical controls [0.44 (0.37 – 0.52)]
 - Adverse effects: diarrhea, LVEF decrease

Immunotherapy in Prostate Cancer

Vaccines

- Vaccine types
 - Dendritic cells
 - Whole cell vaccines
 - Viral vectors
- Tumor associated antigens
 - Prostate specific antigen (PSA)
 - Prostatic acid phosphatase (PAP)
 - Prostate-specific membrane antigen (PSMA)

Sipuleucel-T

- Autologous cells fused with PA2024 (PAP linked to granulocyte-macrophage colony-stimulating factor)
- Placebo-controlled phase 3 trial
- Metastatic, asymptomatic hormone refractory prostate cancer
- 127 patients randomized 2 (Sipuleucel-T):
1 (placebo)

Sipuleucel-T

■ TTP

- Sipuleucel-T: 11.7 weeks
- Placebo: 10.2 weeks
- $P = .052$; HR 1.45 (95% CI: 0.99 – 2.11)

■ Median survival

- Sipuleucel-T: 25.9 months
- Placebo: 21.4 months
- $P = .01$; HR 1.70 (95% CI: 1.13 – 2.56)

■ Results – adverse effects

- Rigors, tremors, fever, “feeling cold”

Allogeneic Cellular Vaccine – GVAX

- Two prostate cancer cell lines modified to express the granulocyte-macrophage colony-stimulating factor gene (GVAX platform)
- 55 patients with asymptomatic, chemotherapy-naïve hormone refractory disease
- Two vaccine doses: 100 million cells (low dose) or 500 million cells (high dose)
- Endpoints were PSA changes, time to progression, and survival

Allogeneic Cellular Vaccine – GVAX

- Median Survival
 - Radiologic group – 26.2 months [95% CI: 17,36]
 - High dose: 34.9 months [95% CI: 8,57]
 - Low dose: 24 months [95% CI: 11,35]
 - Rising PSA group – 37.5 months [95% CI: 29,56]
- Two large phase 3 trials in process
 - VITAL-1 – 600 pts with castrate-resistant, chemotherapy-naïve hormone refractory disease (GVAX vs docetaxel)
 - VITAL-2 – 600 pts with castrate-resistant, chemotherapy-naïve hormone refractory disease (GVAX + docetaxel vs docetaxel)

Updates on Prostate Cancer

Conclusions

- Localized disease
 - Androgen deprivation has questionable role as adjuvant therapy
- Advanced disease
 - The standard first-line treatment is androgen deprivation
 - Patients should be monitored and treated for metabolic syndrome and bone loss
 - Docetaxel-based regimens are first-line treatment for relapsed disease

Updates on Prostate Cancer

Conclusions

- Monitoring response
 - New Working Group Guidelines
 - Circulating tumor cells
- New therapies
 - Satraplatin
 - Angiogenesis inhibitors
 - Vaccines

HOPA/ISOPP 2008

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