Management of advanced prostate cancer: specific considerations for senior adults (1/4)

- First-line androgen deprivation therapy
- First-line chemotherapy
- Docetaxel is the standard of care
- Provides survival advantage in older men
- Weekly regimen for frail patients
- Progression after first-line docetaxel
- Palliative therapy for bone metastases

Androgen deprivation therapy: adverse events

- Bone loss with increased risk of fracture
- Increased risk of diabetes
- Increased risk of fatal cardiac events

Caution in patients with:
- History of stroke
- Chronic heart failure
- Myocardial infarction

LESS IS BETTER!

Docetaxel: survival benefit by age (TAX 327)

<table>
<thead>
<tr>
<th>Age category</th>
<th>Hazard ratio in favour of Docetaxel/Mitoxantrone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 75</td>
<td>ITT</td>
</tr>
<tr>
<td>Age ≥ 75</td>
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</tr>
</tbody>
</table>

ASC 2011
- In men ≥ 75 years, docetaxel q3w & q1w resulted in more dose reductions and discontinuations for adverse events than mitoxantrone
- BUT trend to better improvement in QoL, tumour response and survival with docetaxel q3w

Note: ITT = intention-to-treat.
**Weekly docetaxel plus prednisolone is superior to prednisolone alone in mCRPC**

- **Objective response rate (%)**
  - Docetaxel: 42%
  - Placebo: 28%
- **Median progression-free survival (months)**
  - Docetaxel: 13
  - Placebo: 7.4
- **Overall survival (months)**
  - Docetaxel: 25.1
  - Placebo: 18.8

**Task outcomes**

- **Gastrointestinal grade ≥2**
  - Docetaxel: 9%
  - Placebo: 5%
- **Nail changes**
  - Docetaxel: 27%
  - Placebo: 8%
- **Other/Gastrointestinal grade ≥2**
  - Docetaxel: 37%
  - Placebo: 8%

- **Median age 70 years**
- **No cross-over**

**Management of advanced PCa: specific considerations for senior adults (3/4)**

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- Palliative therapy for bone metastases

**Abiraterone in chemo-naïve patients: an option if approved by regulatory authorities**

- **Radiological PFS**
- **Overall survival**

**Cabazitaxel significantly improves overall survival vs mitoxantrone (TROPIC)**

- **Median age**: 68 years
- **≥75 years**: 18%

**TROPIC: Survival not influenced by age**

- **Overall survival (months)**
  - <75 years: 20
  - ≥75 years: 16

**PATURITY: Prospective registry in men aged 70+ with mCRPC**

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**Favorable tumour grade ≥3 toxicity (%)**

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<td>Fatigue</td>
<td>27.1%</td>
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<td>Nausea/vomiting</td>
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<td>Diarrhoea</td>
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<td>7.3%</td>
<td>0.018</td>
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<td>Anemia</td>
<td>7.6%</td>
<td>6.1%</td>
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<td>Loss of appetite</td>
<td>7.3%</td>
<td>5.3%</td>
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<tr>
<td>Nail change</td>
<td>6.7%</td>
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Abiraterone significantly improves overall survival vs placebo (COU-AA-301)

- Median age: 69 years
- ≥75 years: 28%

Abiraterone vs placebo

<table>
<thead>
<tr>
<th>Median Survival (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone® + Prednisone</td>
<td>11.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.6</td>
</tr>
</tbody>
</table>

1,195 patients with mCRPC who were previously treated with docetaxel.

Specific considerations for senior adults in patients with VERY advanced disease

Cabazitaxel
- Increased risk of febrile neutropenia (7.5 vs 1.3%)
  - Primary prophylaxis with G-CSF recommended in patients aged ≥65 years and/or advanced disease (ESMO guidelines)
- Diarrhoea (6.5 vs 0.3%, grade ≥3)
  - Monitor with antibiotics (as needed)

Abiraterone
- Hypokalaemia, hypertension & fluid retention due to mineralocorticoid excess
  - Hyponatraemia
  - Advocating for discontinuation of daily steroids in concurrent infection or stress
  - Advocating for discontinuation of daily steroids in concurrent infection or stress
  - Hypokalaemia
  - Monitor liver function

COU-AA-301: Survival not influenced by age

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Start treatment</th>
<th>Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>15.8 (13.9-17.4)</td>
<td>0.85 (0.76-0.96)</td>
</tr>
<tr>
<td>Age&lt;br/&gt;≥75</td>
<td></td>
<td>13.7 (11.9-15.6)</td>
<td>0.80 (0.68-0.96)</td>
</tr>
<tr>
<td>Age&lt;br/&gt;&lt;75</td>
<td></td>
<td>16.2 (14.9-17.5)</td>
<td>0.96 (0.85-1.10)</td>
</tr>
</tbody>
</table>

AFFIRM: enzalutamide improves overall survival vs placebo after docetaxel

- Median age: 69 years
- ≥75 years: 25%

Enzalutamide vs placebo

<table>
<thead>
<tr>
<th>Median OS (months)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>19.3</td>
<td>0.85 (0.76-0.96)</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>25.1</td>
<td>1.31 (0.95-1.81)</td>
</tr>
</tbody>
</table>

AFFIRM: Survival not influenced by age

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Activity</th>
<th>Patient Number</th>
<th>Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>842</td>
<td>18.3</td>
<td>0.86 (0.76-0.97)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>≥75</td>
<td></td>
<td>15.7</td>
<td>0.74 (0.65-0.86)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;75</td>
<td></td>
<td>20.5</td>
<td>1.09 (0.96-1.23)</td>
</tr>
<tr>
<td>PSA (mg/dL)</td>
<td>≥20</td>
<td></td>
<td>13.0</td>
<td>0.69 (0.59-0.81)</td>
</tr>
<tr>
<td>PSA (mg/dL)</td>
<td>&lt;20</td>
<td></td>
<td>19.6</td>
<td>1.00 (0.86-1.16)</td>
</tr>
<tr>
<td>CT response</td>
<td>PR/CR</td>
<td></td>
<td>19.5</td>
<td>1.07 (0.88-1.30)</td>
</tr>
<tr>
<td>CT response</td>
<td>PD</td>
<td></td>
<td>12.9</td>
<td>1.35 (1.08-1.67)</td>
</tr>
</tbody>
</table>

ALFSYMPCA: Radium-223 improves survival vs placebo post-docetaxel

- Mean age: 70 years
- Hazard Ratio 0.695

Radium-223 (N=614)

<table>
<thead>
<tr>
<th>Median OS (months)</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11.0</td>
</tr>
<tr>
<td>Radium-223</td>
<td>14.9</td>
</tr>
</tbody>
</table>
Which drug for which patient?

Short response to first-line ADT predicts poor response to abiraterone & enzalutamide

- 108 mCRPC patients after failure of primary ADT
- Treated with secondary hormonal manipulations: abiraterone, DES, ketoconazole, enzalutamide
- Median duration of response to primary ADT: 16 mo [0-118]

<table>
<thead>
<tr>
<th>Duration of response to ADT</th>
<th>≥16 mo</th>
<th>&lt;16 mo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA response</td>
<td>58%</td>
<td>18%</td>
<td>0.01</td>
</tr>
<tr>
<td>PFS rate (median)</td>
<td>5 mo</td>
<td>3 mo</td>
<td>&lt;0.043</td>
</tr>
</tbody>
</table>


TROPIC: Cabazitaxel improves survival whatever the duration of prior ADT

<table>
<thead>
<tr>
<th>Duration of ADT</th>
<th>Median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5 years</td>
<td>Cabazitaxel 20.2 vs Mitoxantrone 17.1, P=0.015</td>
</tr>
<tr>
<td>2.5-4 years</td>
<td>Cabazitaxel 21.0 vs Mitoxantrone 17.7, P=0.03</td>
</tr>
<tr>
<td>≥5 years</td>
<td>Cabazitaxel 19.5 vs Mitoxantrone 15.3, P=0.0031</td>
</tr>
<tr>
<td>Overall</td>
<td>Cabazitaxel 20.2 vs Mitoxantrone 17.1, P=0.015</td>
</tr>
</tbody>
</table>


French ATU: Poor response to abiraterone in patients with high Gleason score

- Abiraterone French ATU program (post-docetaxel setting)
- 408 mCRPC patients enrolled in 19 centers
- Gleason 8-10: 51.2% at diagnosis

- Independent predictive factors of poor response to Abiraterone:
  - Gleason score 8-10
  - Number of chemotherapy lines (>1)


TROPIC: Cabazitaxel improves survival whatever the tumor grade

<table>
<thead>
<tr>
<th>Well/moderately differentiated</th>
<th>Poorly differentiated</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabazitaxel</td>
<td>Mitoxantrone</td>
<td></td>
</tr>
<tr>
<td>N=105</td>
<td>N=109</td>
<td></td>
</tr>
<tr>
<td>P=0.16</td>
<td>P&lt;0.001</td>
<td></td>
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Docetaxel discontinuation for disease progression

- Cabazitaxel
  - Significantly improves OS
  - 44 mCRPC patients treated with first-line docetaxel followed by abiraterone
  - 7/44 patients refractory to docetaxel
  - 0/47 had subsequent PSA, radiological or clinical response to abiraterone


French ATU: ‘temporary authorization for use’
Management of advanced PCa: specific considerations for senior adults (4/4)

- First-line androgen deprivation therapy
- First-line chemotherapy
- Progression after first-line docetaxel
- Palliative therapy for bone metastases
  - Zoledronic acid
  - Denosumab
  - Radiation therapy
  - Experimental radiopharmaceutical: alpharadin

SIOG recommendations for senior adults

- Treatment recommendations for older men with prostate cancer should be based on:

  Health status (mainly driven by co-morbidities)
  AND
  Patient preferences
  OR
  Chronological age

SIOG recommendations for senior adults with PCa

- The urological approach in senior adults should be the same as in younger patients
- Adapt international guidelines (EAU, ESMO, AUA, etc.) to patient health status
- Scientifically established national guidelines are also valid

SIOG recommendations for senior adults

Extended version

<table>
<thead>
<tr>
<th>Health status</th>
<th>Treatment should be adapted to health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit</td>
<td>Same treatment as younger patients</td>
</tr>
<tr>
<td>Vulnerable</td>
<td>Geriatric intervention (or Standard treatment)</td>
</tr>
<tr>
<td>Frail</td>
<td>Geriatric intervention (or Adapted treatment (or palliation))</td>
</tr>
<tr>
<td>Too sick</td>
<td>Only palliation treatment</td>
</tr>
</tbody>
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Treatment should be adapted to health status

Guidelines for localized PCa

- Standard treatment as for younger patients
- Standard treatment as for younger patients (except RP?)
- Symptom management including specific treatments (ADT, TURP, etc.)
- Palliative treatment
Guidelines for advanced PCa

Health status evaluation

Healthy  Vulnerable  Frail  Terminal illness

- Standard chemotherapy
- Standard chemotherapy
- Adapted (weekly?) chemotherapy
- Symptomatic treatment

Hormonal treatment (first & second lines, anti-androgen withdrawal, bisphosphonates/denosumab)

READAPTATION

Droz JP et al. BJU Int 2010;106:462-69

Any questions?