Current concepts in the management of hormone refractory prostate cancer

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Hormone refractoriness Definition

- The presence of evidence of disease progression of a clinical or biochemical nature in the light of castrate serum levels of testosterone (on or off therapy)

The clinical importance of hormone refractoriness in prostate cancer

- Oefelein et al
- Median survival in HRPC with bone metastases 40 months
- Absence of bone metastases- 68 months

Mechanisms of refractory transformation

- Several mechanisms have been proposed
- Significant polymorphism in disease

Sites of hormone resistance

- Pre- receptor
- Receptor
- Post-receptor

Receptor positive /ligand dependent

- Seen in patients on long –term hormonal deprivation therapy
- Selection of malignant clones that express high receptor concentrations for a low level ligand environment
- AR (androgen receptor) gene amplification is rare in primary tumour
- After androgen ablation approximately 30% of tumours become androgen independent due to AR receptor numbers(Feldman and Feldman 2001)
- These patient may respond to total hormone ablation

Increased circulating hormones

- Flutamide binds to AR
- Also binds to receptors in the hypothalamus and pituitary gland
- Interruption of the negative feedback pathway
- GnRH levels are increased leading to chronic hyperstimulation of the testes with increased androgen levels
- ? Effect of withdrawal therapy response

Increased endogenous hormones

- In pts on long term androgen ablation , selection of tumour cells with higher 5 alpha reductase activity
- Increased DHT produced in the adrenal glands
- Increased intracellular DHT compensates for the low level of circulating testosterone
- Men of African descent have higher incidence of polymorphism of 5 alpha reductase gene and similar higher incidence of poor prognosis prostate cancer (Ruijter et al)

Receptor hypersensitivity

- Upregulation of AR sensitivity to low circulating androgen levels
- Other signalling pathways vimplicated
- Ras, MAPK

Co-regulator mechanisms

- Nuclear and steroid receptors –co-activators and co-repressors
- Ratio determined
- SRC-steroid receptor co-activator family implicated
- SRC-1 higher levels of disruption associated with recurrence
- SRC-1,2 associated with increased androgen sensitivity

Receptor positive /ligand independent

- Receptor mutation – at diagnosis and post therapy
- Alteration of the affinity of the AR
- AR mutation of metastases increased in metastatic vs primary tumour
- Noted in patients on bicalutamide
- ? Role of withdrawal of this agent

AR /Growth factor cross talk

- EGFR family
- IGF-1
- Keratinocyte growth factor
- IL-6

Bypass mechanisms

- Alternative pathways may bypass the primary pathway
- Bcl-2 overexpression
- P53 mutation

Receptor negative hormone independent

- DNA hypermethylation leads to receptor resistance

Therapies of HRPC

- Specific hormonal manipulation
- Chemotherapy
- Adjunctive therapiesMultimodal therapies

Observation

- May initially be utilized
- In poor performance status patients

Hormonal manipulation

- Total androgen suppression
- Withdrawal therapy
- Second –line hormonal therapies
- Ketoconazole
- Prednisone
- Dexamethasone
- Oestrogens

Chemotherapy

- Initially noadvantage of chemotherapy vs best supportive care
- Agents-5-FU, Etoposide ,mitoxantrone
- Oncology/Urology in accord
- Standard of care was Mitoxantrone and prednisone

SWOG 9916

- Established standard of care
- Estramustine and docetaxel vs Mitoxantrone /prednisone
- Primary EP was overall survival
- Powered for a 33% OS
- Secondary end points were PFS, PSA response and measurable disease

Patient profile

- Elevated PSA
- Bone pain
- Excellent performance status

Results

- Achieved 23% improvement in OS
- Risk of death was reduced by 20% HR=.8
- PFS 6.3 mos vs 3.2 mos

Toxicity

- Neutropenia
- Nausea
- vomiting
- CVS events
- Neurology
- Metabolic

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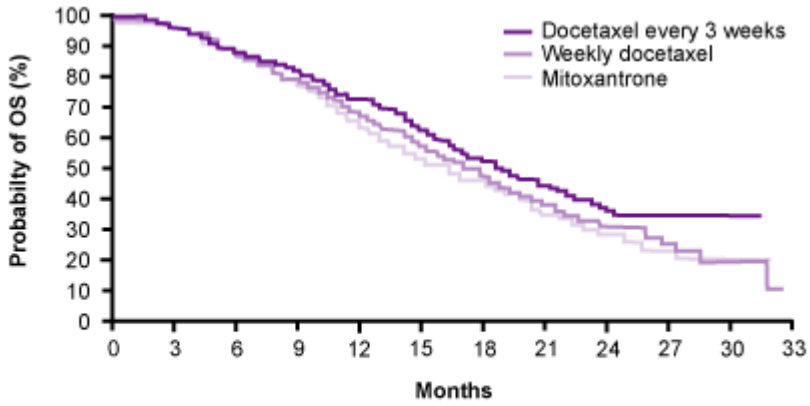
- Docetaxel and prednisone (2 schedules) vs mitoxantrone
- OS primary EP
- Secondary EP Quality of life, PSA , pain evaluation
- Median PSA
- 90% bone disease



No. at Risk						
Docetaxel every 3 weeks	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Results

- OS 18.9 mos vs 16.5 mos P .009
- HR.76
- >50 % reduction of PSA Improved quality of life
- More neutropenia , alopecia, peripheral neuropathy
- Has become the standard of care for HRPC

Docetaxel resistance

- New taxane
- Cabazitaxel
- 15.1 mos vs mitoxantrone 12.7 mos
- Indicated for second line

New agents

- Radium 223 –Alpharadin
- Medivation –Androgen inhibitor
- Sipuleucel-T
- Calcitriol
- G-CSF
- Likely used in a tiered manner

Supportive care

- Pain management
- Bisphosphonates
- Psychological Support
- Radiotherapy-EBRT
- Strontium

Investigational protocols

- Encourage patients to enrol

Conclusion

- Polymorphous disease
- Much progress has been made in understanding biology
- Clinician must be aware of the current options available to the patient
- Treatment is multidisciplinary

Thank you