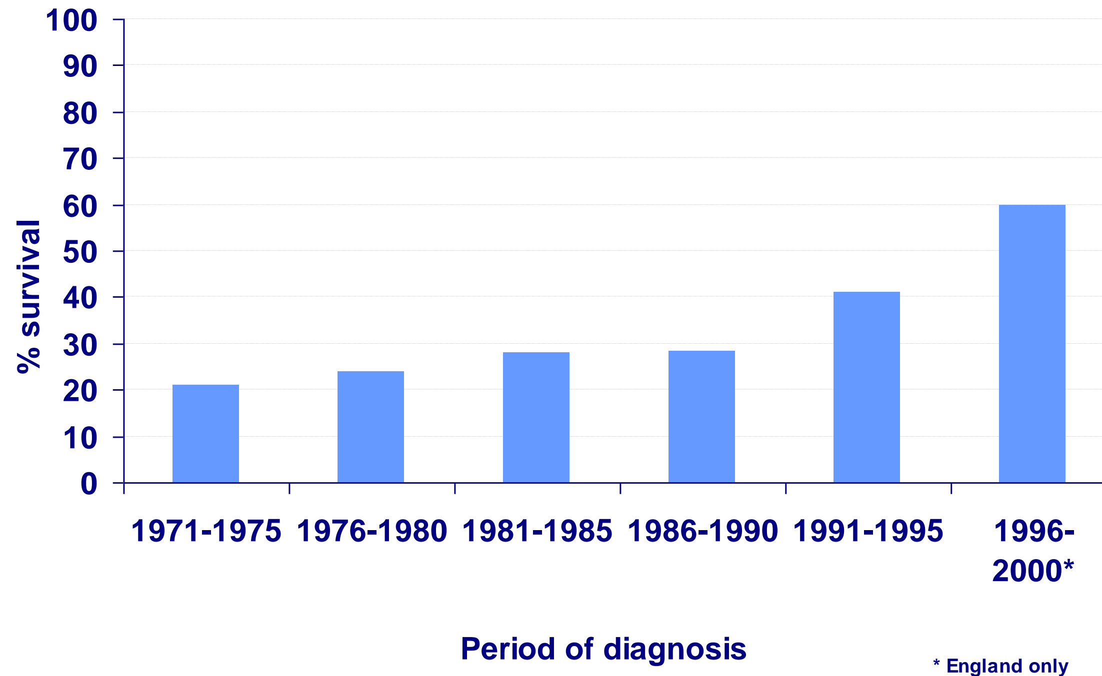
The Role of Chemotherapy in Advanced Prostate Cancer

BAUN Meeting

Maryon Hardie

June 2010

Prostate Cancer: A Chronic Disease?



- Earlier diagnosis
- Better treatment (localised and advanced disease)
- 20-30% present with incurable metastatic disease

Definitions

Castrate Refractory Prostate Cancer (CRPC)

- Disease deteriorating despite ongoing castration therapy

Metastatic CRPC (mCRPC)

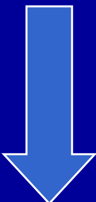
- CRPC with evidence of disease outside prostate

Hormone Refractory Prostate Cancer (HRPC)

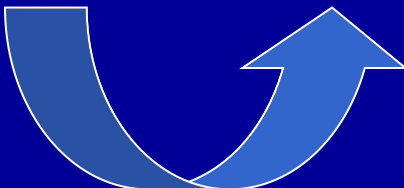
- Disease not controlled by any hormone-related treatment

Hormonal Dependent Prostate Cancer

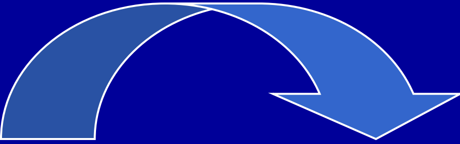
Pituitary



Testes



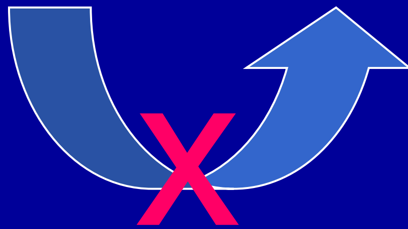
Testosterone



Tumour Growth

Pituitary

Testes



X

Testosterone

Tumour
Growth

Surgery

Pituitary

Zoladex

Testes

Testosterone

Tumour
Growth

Androgen deprivation – median survival 2.5 years

80% patients have symptomatic benefit

Why does castration therapy fail?

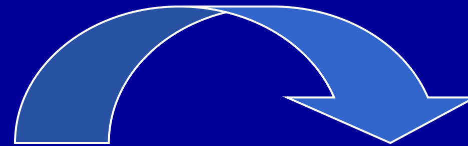
- Prostate cancer usually responds to androgen deprivation therapy initially
- On average, malignant cells become resistant after 12-18 months
- Despite being “hormone refractory”, prostate cancer cells have high androgen receptor expression

Extra-gonadal androgens

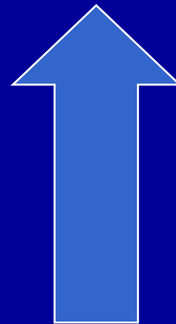
Pituitary

Testes

Testosterone



Tumour Growth



Adrenal glands

Barriers to chemotherapy

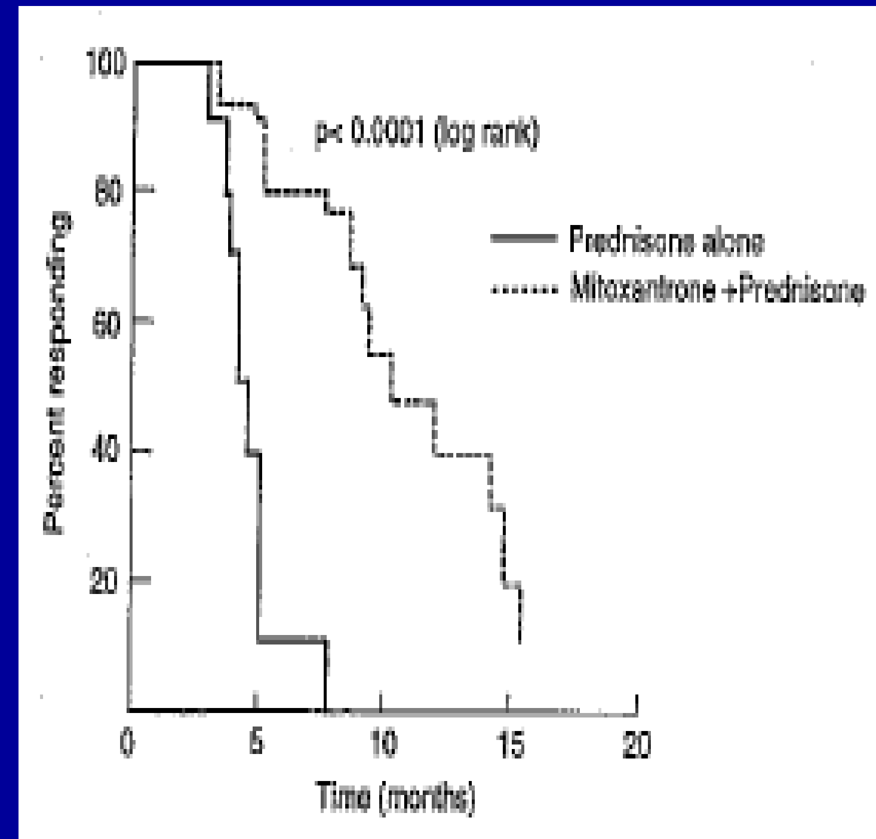
- Elderly population
- Co-morbidities
- Reduced marrow reserve

The Advent of Chemotherapy

- 1996: Mitoxantrone + Prednisolone vs Prednisolone
- Palliative end points:
  - Decreased pain
  - Decreased analgesic use
  - Duration of response

The Advent of Chemotherapy

- 1996: Mitoxantrone + Prednisolone vs Prednisolone
- Palliative end points:
  - Decreased pain
  - Decreased analgesic use
  - Duration of response



Tannock et al *JCO* 1996

The Advent of Chemotherapy

- 1996: Mitoxantrone + Prednisolone vs Prednisolone
- Palliative end points:
  - Decreased pain
  - Decreased analgesic use
  - Duration of response
- Decrease in PSA did not distinguish those who had palliative response
- Mitoxantrone + Prednisolone did not improve overall survival

Docetaxel

- Chemotherapy made from Yew trees
- Also used in breast and lung cancer
- 3-weekly infusion (1hr)
- £1000 per dose
- Given with prednisolone 5mg bd
- Pre-medication with high dose dexamethasone

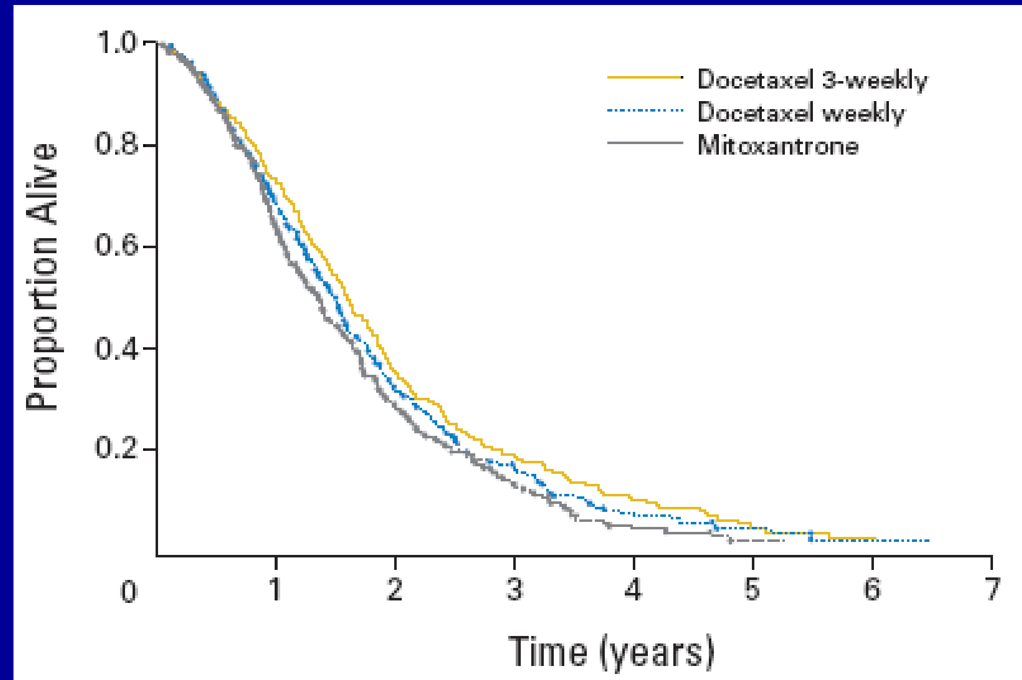
Docetaxel side effects

- Definite:
  - Low white blood count
  - Fatigue
- Common:
  - Alopecia
  - Mild nausea
  - Infusion reaction
- Rare:
  - Neuropathy
  - Neutropenic sepsis
  - Mouth ulcers
  - Diarrhoea
  - Anaphylaxis

Docetaxel (Taxotere)

- TAX 327 study (2004)

- 3-weekly docetaxel
- Weekly docetaxel
- 3-weekly mitoxantrone



Tannock et al *JCO* 2004

Benefits of Docetaxel

- Median Survival
  - 3-weekly Docetaxel: 18.9 months
  - Mitoxantrone: 16.5 months

- Pain reduction: 35 vs 22%
- 50% PSA reduction: 45 vs 32%
- Improved QoL: 22% vs 13%

Unanswered Questions

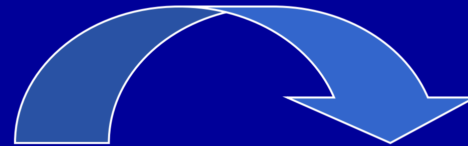
- When to treat?
  - e.g. asymptomatic patient with rising PSA
- What next?
  - Prednisolone
  - Stilboestrol
  - Docetaxel rechallenge
  - Other chemo
  - New agents
  - Clinical Trials

Extra-gonadal androgens

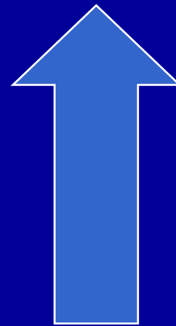
Pituitary

Testes

Testosterone



Tumour
Growth



Adrenal glands

Pituitary

Testes

Testosterone

Tumour
Growth

Abiraterone

Adrenal glands

Abiraterone

- Blocks adrenal androgen production
- 45% of patients had >50% PSA fall
- No major toxicities
- Median time to progression was 161 days
- Phase III trials ongoing

Other new agents

- Cabazitaxel:
  - a next-generation taxane
  - selected to overcome the emergence of taxane resistance
  - Survival benefit post-docetaxel

Case Study

- 78yr old.
- Previous rectal surgery – neurogenic bladder, AF
- 2000: "well differentiated" adenoCa
  extending through capsule
  iPSA 46
- Neoadjuvant hormones ⟶ PSA 3
- EBRT and ongoing Zoladex

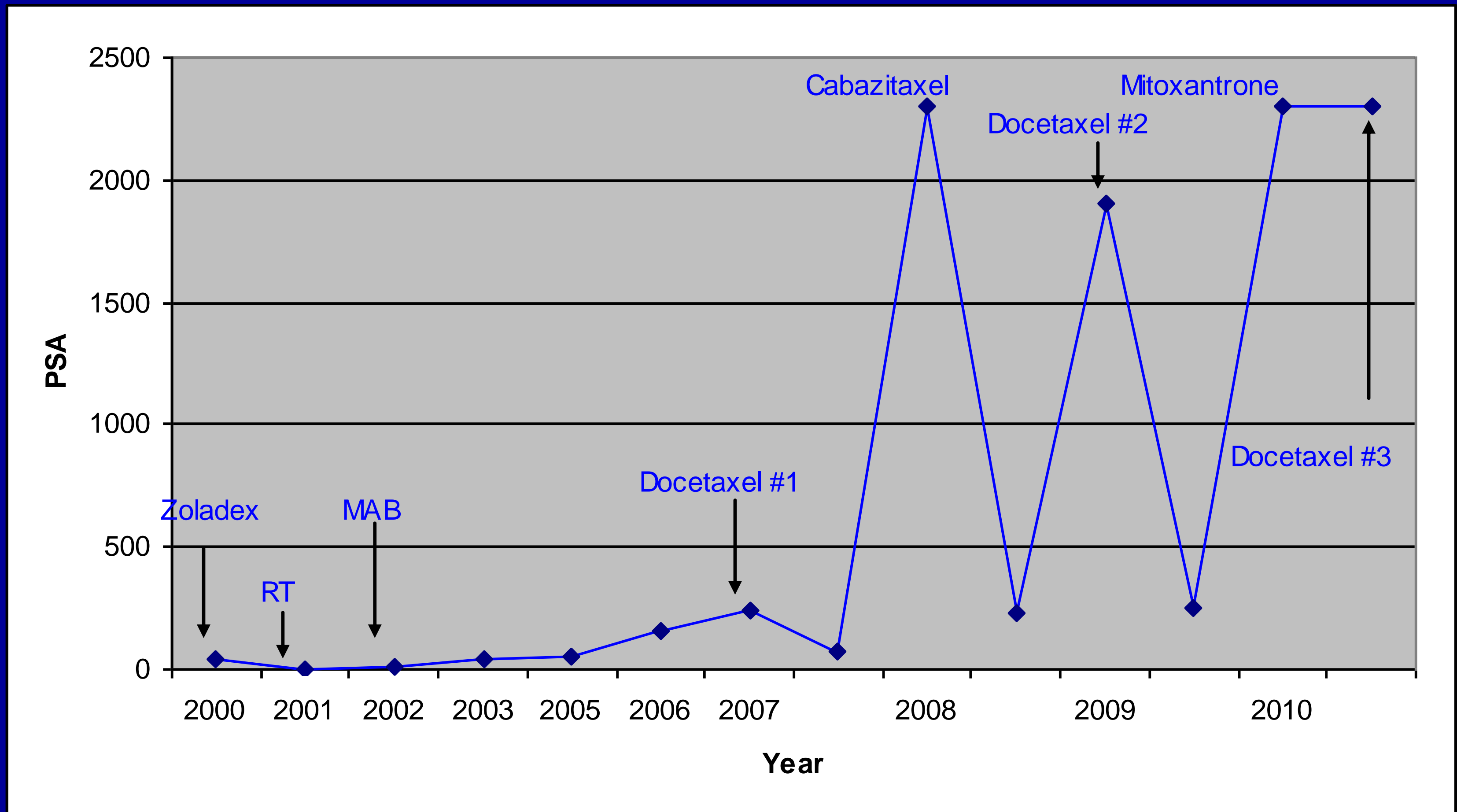
Case Study

- May 2002: PSA 9
  - Maximum androgen blockade
- Nov 2002: PSA 37 (no withdrawal response)
  - Imaging shows local recurrence
  - Not for surgery or cryotherapy
  - Ethinyloestradiol
- April 2005: PSA 48
  - MRI: extensive lymphadenopathy
- April 2006: PSA 160 (but fluctuating)
  - Patient well
- January 2007: PSA 238
  - Lymphoedema
  - Clinical trial: Randomised to docetaxel

Case Study

- April 2008: R hydronephrosis stented
- July 2008: TROPIC study
  - Randomised to Cabazitaxel
  - Neutropenic sepsis
  - Hepatic toxicity
  - Good clinical response
- March 2009: PSA 1600
  - Docetaxel rechallenge (6 cycles) → PSA 250
- January 2010:
  - Clinical, biochemical and radiological progression
  - Mitoxantrone (5 cycles) – disease progression
- May 2010:
  - Docetaxel rechallenge

Timecourse of Castrate Refractory disease



Summary

- Hormone refractory prostate cancer is an incurable condition and symptomatic management is the priority
- Chemotherapeutic agents now provide a survival advantage, in addition to palliative benefits, with manageable toxicity
- New agents on the horizon may be of clinical relevance to current patients