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## Evidence-based Series #3-15: Section 1

# Non-Hormonal Systemic Therapy in Men with Metastatic Hormone-Refractory Prostate Cancer: A Clinical Practice Guideline

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A Quality Initiative of the  
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)  
Developed by the Genitourinary Cancer Disease Site Group

**Report Date: November 1, 2005**

### Question

Which non-hormonal systemic therapies are most beneficial and should be recommended for the treatment of hormone-refractory prostate cancer?

First-line cytotoxic and non-cytotoxic systemic therapies are the agents of interest. Overall survival, disease control (as assessed by measures such as progression-free survival, time-to-progression, time-to-treatment failure, and objective and prostatic-specific antigen [PSA] response rates), palliative response rate, quality of life, and toxicity are the outcomes of interest.

### Target Population

These recommendations apply to men with progressive hormone-refractory prostate cancer and evidence of metastases.

### Recommendations

- For men with clinical or biochemical evidence of progression and evidence of metastases, treatment with docetaxel 75 mg/m<sup>2</sup> administered intravenously every three weeks with 5mg oral prednisone twice daily should be offered to improve overall survival, disease control, symptom palliation, and quality of life.
- Alternative therapies that have not demonstrated improvement in overall survival but can provide disease control, palliation, and improve quality of life include weekly docetaxel plus prednisone, and mitoxantrone plus prednisone (or hydrocortisone).

### Qualifying Statements

- Docetaxel-based chemotherapy is the only treatment that has demonstrated an overall survival benefit in men with hormone-refractory prostate cancer.
- The timing of docetaxel therapy in men with evidence of metastases but without symptoms should be discussed with patients and individualized based on their clinical status and preferences.
- In the largest randomized trials reviewed for this guideline, the men enrolled continued on

gonadal androgen suppression and discontinued the use of antiandrogens. These manoeuvres are recommended for men with hormone-refractory prostate cancer who receive chemotherapy.

- Men with hormone-refractory prostate cancer should have symptom control optimized.
- Use of estramustine in combination with other cytotoxic agents is not recommended due to the increased risk of clinically important toxicities without evidence of improved survival or palliation.

### **Key Evidence**

- Twenty-eight randomized controlled trials of non-hormonal systemic therapy met the eligibility criteria of this review. Twenty of those trials studied cytotoxic and eight studied non-cytotoxic drug regimens. No published systematic reviews or evidence-based guidelines were identified.
- Two recent, large trials have reported improved overall survival with combination docetaxel (75mg/m<sup>2</sup> intravenously every three weeks) over mitoxantrone-prednisone:
  - In a three-arm trial (n=1006) (1), improved median survival was found for docetaxel-prednisone administered every three weeks compared with mitoxantrone-prednisone (median survival, 18.9 versus 16.5 months; two-sided p=0.009), but no statistically significant survival benefit was observed with docetaxel-prednisone given on a weekly schedule. Improvements in palliative and quality-of-life response were observed with both docetaxel-prednisone regimens. The docetaxel-prednisone arms were associated with more frequent mild toxicities and similar rates of serious toxicities compared with mitoxantrone-prednisone.
  - In the second trial (n=666) (2), survival time was longer with docetaxel-estramustine compared with mitoxantrone-prednisone (median survival, 17.5 versus 15.6 months, respectively; two-sided p=0.02). Estramustine combined therapy was associated with greater grade 3-4 toxicity (54% versus 34%) and more toxic deaths (seven versus two) than mitoxantrone-prednisone.
- The docetaxel trials provide indirect evidence of similar efficacy and increased toxicity with the addition of estramustine to docetaxel.
- Mitoxantrone plus corticosteroid compared with corticosteroid alone has been evaluated in three trials and shown improved palliative and pain response, quality of life, and/or improved time-to-disease progression compared with initial corticosteroid therapy alone. These trials have not shown improvements in survival. Toxicity attributable to mitoxantrone was minimal, and cardiomyopathy was observed in ≤5% of patients.
- Single randomized trials have reported improved time-to-progression with estramustine-vinblastine versus vinblastine alone and vinorelbine-hydrocortisone versus hydrocortisone alone and improved time-to-progression and pain response with suramin-hydrocortisone compared with placebo-hydrocortisone.

### **Treatment Alternatives**

- There is less evidence of a clinical benefit in men with hormone-refractory prostate cancer treated with estramustine plus vinblastine, suramin plus hydrocortisone, and vinorelbine plus hydrocortisone compared to docetaxel alternatives. Routine use of those regimens is not recommended.
- Non-cytotoxic therapies studied in randomized trials including liarozole, atrasentan, and APC8015 should not be used outside the setting of a clinical trial.
- Expectant management, trials of secondary hormonal manipulations, and/or participation in clinical trials may be reasonable alternatives for patients on an individualized basis.

- Use of bisphosphonates and radioisotopes may be an option for patients with hormone-refractory prostate cancer and are addressed in separate guidelines (see below).

### **Related Guidelines**

- Practice Guideline Report #3-6: *Use of Strontium89 in Patients with Endocrine-Refractory Carcinoma of the Prostate Metastatic to Bone*
- Practice Guideline Report #3-14: *The Use of Bisphosphonates in Men with Hormone-Refractory Prostate Cancer*
- Practice Guideline Report #13-2: *Radiotherapy Fractionation for the Palliation of Uncomplicated Painful Bone Metastases*
- Practice Guideline Report #14-1: *Radiopharmaceuticals for the Palliation of Painful Bone Metastases*

### *Funding*

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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## REFERENCES

[Numbers in brackets refer to Section 2 References.]

1. Tannock IF, De Wit R, Berry WR, Horti J, Pluzanska A, Chi K, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351:1502-12. [4]
2. Petrylak D, Tangen C, Maha PH, Hussain M, Lara PN, Jones J, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004;351:1513-20. [62]