# Chemotherapy in the treatment of prostate cancer

## Is there a role?

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**BACKGROUND**
Prostate cancer is a common cancer in men. Traditional therapies are effective except in patients who progress to hormone refractory disease. Historically, chemotherapy has had a limited role in the treatment of prostate cancer. However, new agents are showing promise in patients with advanced disease.

**OBJECTIVE**
This article reviews and presents current evidence on the use of chemotherapy in the treatment of prostate cancer and attempts to aid general practitioners in their role in the multidisciplinary environment of current cancer care.

**DISCUSSION**
Analysis of the literature suggests there is no clear role for chemotherapy in the neoadjuvant or adjuvant setting. Chemotherapy may provide a short survival benefit in men with androgen independent prostate cancer but more importantly, can improve quality of life, and reduce pain and prostate specific antigen thus providing effective palliation.

**Prostate cancer is one of the most common cancers in men and the incidence increases with age from 0.4 per 100 000/year in men under 45 years of age to 270 per 100 000/year in men over 65 years of age.[1] Patients with localised disease benefit from radical surgery or radiotherapy while patients with locally advanced or metastatic disease traditionally receive radiotherapy or androgen deprivation therapy (ADT).[2] Although most patients initially respond to ADT, many with advanced disease often develop cancers that are hormone or androgen independent, rendering ADT ineffective. Men who develop hormone independent disease have a median survival of approximately 1 year.[3] Systemic chemotherapeutic agents have been long available to treat patients with prostate cancer and particularly, men whose cancers are unresponsive to ADT.**

In this article we examine the role of chemotherapy in the different stages of prostate cancer. Our aim is to provide general practitioners with current information about the role of chemotherapy in prostate cancer. This is an important area, as the number of men with advanced prostate cancer is increasing. While chemotherapy is given in the hospital setting, the GP has a key role in the multidisciplinary oncology team, caring for patients with whom they have often shared an extended therapeutic relationship. Currently chemotherapy is only of benefit as a palliative treatment and it is essential that the patient's GP is well informed and involved in care at this critical time.

## Who is suitable for radical therapy?

Men with T1 and T2 disease (*Table 1*) are usually treated with radical surgery or radiotherapy. However, patients with T3 and T4 disease or a prostate specific antigen (PSA) over 10–20 ng/mL (depending on surgeon's preference) are usually not considered for radical prostatectomy as the risk of metastatic disease is too high. Depending upon a range of individual factors, these patients may be treated with a combination of radiotherapy and/or ADT.[1,2] With time, patients may develop androgen independent disease and in this setting there is currently no effective treatment. Chemotherapeutic agents are being evaluated and may provide effective palliation.[4,5]

## Methods

The current literature on the role of chemotherapy in low and high risk prostate cancer was reviewed by searching the MEDLINE database from 1966 to March 2006. We reviewed approximately 60 articles. In particular, we primarily selected recent English language review articles that discussed the role of modern chemotherapeutic agents in patients with prostate cancer.

**Table 1. Classification of prostate cancer**

| | |
|---|---|
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| T1a | Tumour found in tissue removed at TUR (<5% is cancerous or histological grade <7) |
| T1b | Tumour found in tissue removed at TUR (>5% is cancerous or histological grade >7) |
| T1c | Tumour identified by prostate needle biopsy for elevated PSA |
| T2a | Tumour involves less than half of one lobe |
| T2b | Tumour involves more than half of a lobe, but not both lobes |
| T2c | Tumour involves both lobes |
| T3a | Unilateral extra capsular extension |
| T3b | Bilateral extra capsular extension |
| T3c | Tumour invades seminal vesicles |
| T4 | Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall |

## Discussion

Men with prostate cancer can be stratified into three groups:

- those with local disease being treated with radical surgery or radiotherapy – is there a place for neoadjuvant therapy?
- those who have had radical treatment and seek further preventive therapy – is there a place for adjuvant therapy?
- those with advanced disease – is palliative chemotherapy available?

The role of chemotherapy at each of these stages is being investigated by different groups. Evidence to date of clinical relevance is presented.

### Neoadjuvant chemotherapy

The goal of neoadjuvant therapy is to diminish cancer load before 'definitive' treatment (ie. surgery or radiotherapy) and to reduce recurrence rates by targeting micrometastases that may lead to failure of local treatment. Androgen deprivation therapy has offered no survival benefit when used as neoadjuvant therapy for localised prostate cancer.[6–8] Neoadjuvant chemotherapy may reduce PSA levels before surgery or radiotherapy[9,10] but does not improve survival.[11,12] The Cancer and Leukaemia Group B are performing a randomised control trial of 750 men comparing neoadjuvant estramustine and docetaxel with radical prostatectomy compared to radical prostatectomy alone (CALGB 90203).[13] The results are not yet available. Currently, there is no conclusive evidence for the role of neoadjuvant chemotherapy in the treatment of prostate cancer before radical therapy. Further studies are required with larger numbers and longer term follow up.

### Adjuvant chemotherapy

The aim of adjuvant chemotherapy is similar to neoadjuvant chemotherapy but is focused on trying to eradicate micrometastatic disease and improve outcome. Currently there is little published data on adjuvant chemotherapy after radical prostatectomy or radiotherapy. Presently, there are two trials, SWOG9921 and RTOG 9902, evaluating the survival benefits of adjuvant chemotherapy postradical prostatectomy and postradiotherapy respectively.[14,15] Adjuvant chemotherapy is promising, but studies with larger patient numbers and longer term follow up are required. Currently, there is no evidence based role for adjuvant chemotherapy in the treatment of prostate cancer.

### Chemotherapy in advanced disease

Despite the lack of randomised evidence, the role of ADT is well established in the treatment of advanced disease and remains the mainstay of treatment for men with advanced prostate cancer. Experience with chemotherapy had been disappointing until recently.[16,17] Chemotherapy can reduce pain,[18,19] PSA levels and improve quality of life and palliation.[4,5,20] Prostate specific antigen decline cannot be used as an indicator of increased survival but TAX327[5] and SWOG9916[4] are key recent studies that have demonstrated a survival benefit from chemotherapy in patients with advanced androgen independent disease.

The SWOG9916 study is a randomised controlled phase III clinical trial that compared docetaxel and estramustine against mitoxantrone and prednisone in 674 patients with hormone independent prostate cancer. The investigators found a statistically significant 1.9 month advantage in median survival for patients who received docetaxel with estramustine.[4,21] TAX327 is a phase III randomised controlled trial comparing the effects of docetaxel and prednisone with mitoxantrone and prednisone in 1006 patients. This trial showed that docetaxel given every 3 weeks provided a 2.5 month benefit in median survival in men with advanced disease.[5] Again, this was statistically significant. These are the first two studies of any type to have demonstrated a clear survival benefit in men with advanced prostate cancer.

Docetaxel can have a significant side effect profile; grade 3 and 4 toxcities are listed in *Table 2*.[5] However, it has been used by medical oncologists in Australia for the past 10 years, mainly for breast cancer. Lower grade toxicities are more common (fatigue, alopecia, diarrhoea, myalgia) and there is a great deal of experience in managing these side effects, both major and minor. Clearly, the risk-benefit ratio should be considered before commencing docetaxel therapy. Ideally men would have reasonable performance status before commencing docetaxel and therapy needs to be ceased if major toxicities occur. At this stage docetaxel is a palliative treatment only and should be commenced in patients with androgen independent prostate cancer.

## Conclusion

The role of chemotherapy in treating patients of different stages of prostate cancer is still an area of active investigation. To date there is no evidence to support the widespread use of chemotherapy in the neoadjuvant or adjuvant setting, except in clinical studies. This may change once results of CALGB 90203, SWOG9921 and RTOG9902 become available. Docetaxel has demonstrated a survival benefit in patients and could be considered the treatment of choice for patients with androgen independent disease. Other agents such as mitoxantrone and prednisolone are helpful in

**Table 2. Severe adverse events (grades 3 and 4) that occurred with 3 weekly docetaxel use[18,22]**

| Condition | Incidence |
|---|---|
| Anaemia | 5% |
| Thrombocytopenia | 1% |
| Neutropenia | 32% |
| Fatigue | 53% |

symptom control and PSA response but they have not yet demonstrated a survival benefit. It is clear that chemotherapy has a role in the palliative treatment of advanced prostate cancer, and as a result of the docetaxel studies, there is intense interest in developing better agents and combinations.

## Summary of important points

- Presently there is no clear role for adjuvant or neoadjuvant chemotherapy in the treatment of prostate cancer.
- Docetaxel confers a survival benefit in patients with androgen independent prostate cancer and has a role in palliation in these patients, but it may have significant side effects and the risk-benefit ratio must be taken into consideration before initiating treatment.

Conflict of interest: none declared.

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