Hormone-refractory prostate cancer: what have we learned?

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INTRODUCTION

Much research has been conducted in the past 20 years on hormone-refractory prostate cancer (HRPC) and its treatment. Clinical factors that affect outcomes have been identified, and these findings have led to more accurate prognoses for individual patients. Chemotherapy regimens that significantly prolong the survival of patients with metastatic HRPC have been developed. These and other advances have changed the approach to the management of HRPC, and ongoing research is likely to yield further improvements in patient care.

PSA PROGRESSION

There are several treatment options for patients who have an increase in PSA level despite maintaining castrate levels of androgen (Fig. 1) [1]. Because these patients might still have hormone-dependent disease, modifying their current hormone therapy is often appropriate, but a complete withdrawal can hasten disease progression and decrease survival. The addition of antiandrogens to LHRH analogues, if not previously prescribed, results in a PSA response (>50% reduction) in 60–80% of patients, with a median duration of response of 4–6 months [1]. A change or withdrawal of antiandrogen treatment results in a PSA response in a further 25–40% of patients, with an expected response duration of 4–6 months. Secondary hormone manipulation, e.g. by using adrenal testosterone inhibitors, low-dose diethylstilbestrol, or steroids, reduces PSA levels in 40–60% of patients, with a median response duration of 4–8 months.

It was recently reported that patients with rising PSA levels despite castrate levels of testosterone appear to have a relatively good prognosis, with a median survival of 68 months without metastases, or 40 months with metastases (Fig. 2a) [2]. The favourable prognosis reflects the early diagnosis of hormone resistance by means of PSA measurement.

HRPC

Patients who continue to have increased PSA levels despite secondary hormone manipulation have HRPC. The definition of HRPC remains a topic of debate. According to the most recent guidelines produced by the European Association of Urology (EAU), a patient must meet the following criteria to be considered as having HRPC:

- maintained castrate levels of serum testosterone;
- three consecutive PSA increases 2 weeks apart that result in two 50% increases over the nadir;
- PSA progression despite antiandrogen withdrawal for ≥4 weeks or secondary hormone manipulation;
- progression of osseous or soft tissue lesions.

Using the definition described above, the mean survival period for patients with HRPC is 6–20 months, depending on characteristics at presentation such as the presence and extent of metastases [1]. This striking difference in outcome from that of patients with an increasing PSA level alone confirms that HRPC, by the above definition, is a particularly late stage of disease.

CONTINUED ANDROGEN SUPPRESSION IN HRPC

A literature review reported in 1993 noted that ~20% of patients entering clinical trials of chemotherapy for HRPC have not had orchidectomy; <10% of studies specified whether androgen suppression should be continued in these patients [3].

The current EAU guidelines recommend continued androgen suppression in patients not treated by orchidectomy and with HRPC, although few studies have addressed the benefits of this approach. The EAU recommendation was based primarily on evidence reported by Manni et al. [4], who conducted a small randomized trial to determine whether androgen priming potentiates the cytotoxic effects of chemotherapy. In all, 85 men with disease progression despite orchidectomy were randomly selected to receive androgen priming or chemotherapy alone. The median survival of men who received androgen priming (10 months) was significantly worse than that of men who did not (15 months; \( P = 0.009 \)), a result indicating that continuous androgen blockade might be beneficial in men with HRPC.

Two retrospective studies were conducted on the basis of pooled data from many trials, in an effort to evaluate the benefit from continuous androgen blockade in HRPC. The two independent studies produced conflicting results. Hussain et al. [5] reviewed data from 205 men who participated in five phase II trials conducted by the Southwest Oncology Group (SWOG). These men received chemotherapy with continued androgen suppression (orchidectomy patients, 172) or no further androgen suppression (no orchidectomy, 33). There was no significant difference in median survival between the groups (7 vs 6 months; \( P = 0.73 \)). By contrast, Taylor et al. [3] found a modest survival advantage for men who had continued androgen suppression, in a review of data from 341 men who participated in four phase II and III trials conducted by the Eastern Cooperative Oncology Group. The results of both studies should be interpreted cautiously, given their retrospective nature. Currently men with HRPC and no orchidectomy should continue to receive androgen suppression therapy indefinitely, given the modest potential benefit and minimal risks associated with this approach.

CYTOTOXIC CHEMOTHERAPY

Patients with HRPC are eligible for other than hormone therapy, e.g. chemotherapy. According to the EAU, chemotherapy can be initiated after documenting two consecutive increases in PSA level above a previous reference level [1]. Patients should have a PSA
In a large, international three-arm study, docetaxel plus prednisone was weighed for each case. and risks of cytotoxic chemotherapy should be considered for patients with HRPC, although the benefits of chemotherapy is the treatment of choice for patients with metastatic disease.

Two pivotal studies showed the clinical efficacy and safety of docetaxel-based chemotherapy in patients with metastatic HRPC [6,7]. The results of these studies suggest that docetaxel-based cytotoxic chemotherapy is the treatment of choice for patients with HRPC, although the benefits and risks of cytotoxic chemotherapy should be weighed for each case.

DOCETAXEL PLUS PREDNISONE

In a large, international three-arm study (TAX-327), = 1000 patients with HRPC were randomly selected to receive mitoxantrone every 3 weeks, docetaxel every 3 weeks, or weekly docetaxel. All patients received prednisone [6]. The median age was 68 years and = 20% of patients were aged ≥75 years; >90% had bone metastases, ≈ 23% had visceral disease and ≈ 45% had pain at baseline.

After a median follow-up of = 20 months, patients who received docetaxel every 3 weeks had a median survival (18.9 months) that was significantly longer than that of patients who received mitoxantrone (16.5 months; P = 0.009) but similar to that of patients who received weekly docetaxel (17.4 months; P = 0.36; Fig. 2b). Compared with patients who received mitoxantrone, those who received docetaxel on either schedule had improved pain control and quality of life. However, the incidence of adverse events was higher in those who received docetaxel every 3 weeks than in those who received mitoxantrone. The primary adverse events were grade 3 or 4 neutropenia, diarrhoea and neuropathy.

DOCETAXEL PLUS ESTRAMUSTINE

In a second study conducted by the SWOG, 674 patients with histologically confirmed metastatic HRPC were randomly selected to receive docetaxel plus estramustine or mitoxantrone plus prednisone [7]. Unlike patients in the TAX-327 trial, patients in the SWOG study were required to have measurable disease at baseline. The median age was 70 years, and the median baseline PSA level was relatively high (84 ng/mL in the docetaxel/estramustine group and 90 ng/mL in the mitoxantrone/prednisone group); = 86% had bone involvement and 36% had bone pain of grade 2 or greater at baseline.

After a median follow-up of 32 months, patients given docetaxel plus estramustine had a significantly greater median survival than did those given mitoxantrone plus prednisone (17.5 vs 15.6 months; P = 0.02; Fig. 2c). The median time to progression was also significantly greater in patients who received docetaxel plus estramustine (6.3 vs 3.2 months; P < 0.001). The rate of pain relief was similar in the two treatment groups. Patients given docetaxel plus estramustine had a higher incidence of serious adverse events, including grade ≥ 3 febrile neutropenia (5% vs 2%; P = 0.01), nausea and vomiting (20% vs 5%; P < 0.001), and cardiovascular events (15% vs 7%; P = 0.001).

The median survival of patients who received the docetaxel/estramustine regimen was similar to that previously reported with docetaxel alone. The clinical benefit of estramustine, which is associated with an increased risk of cardiovascular events, is therefore questionable. Currently the combination of docetaxel and prednisone is considered standard first-line therapy for HRPC, given its demonstrated ability to prolong overall survival.

In an effort to improve the toxicity profile of the docetaxel/estramustine regimen, an intermittent schedule of administration was recently evaluated in a multicentre phase II study [8]. In all, 75 patients (median age 66 years) with HRPC and PSA or clinical progression received weekly docetaxel (35 mg/m² on days 2, 9 and 16) and estramustine (140 mg three times daily on days 1–3, 8–10 and 15–17) for three cycles (one sequence). Treatment was then suspended until PSA levels doubled or progression was otherwise suspected, at which point the patients had a second sequence. Overall, the PSA response rates after sequences 1, 2, 3 and 4 were 766, 80%, 57% and 29%. The median treatment-free intervals after sequences 1, 2 and 3 were 86.5,
FIG. 2.

a, The median survival of patients with or without metastases who have rising PSA levels despite castrate levels of testosterone (redrawn using data from Oefelein et al. [2]); b, Overall survival of patients with metastatic HRPC treated with docetaxel given every 3 weeks (q3w), weekly docetaxel, or mitoxantrone, in the TAX-327 trial. All patients received prednisone. Adapted with permission from Tannock et al. [6]; copyright 2004, Massachusetts Medical Society.) OS, overall survival; c, Overall survival of patients with metastatic HRPC treated with docetaxel plus estramustine (D + E) or mitoxantrone plus prednisone (M + P) in the SWOG 99–16 trial. Adapted with permission from Petrylak et al. [7]; copyright 2004, Massachusetts Medical Society. OS, overall survival.
86.0 and 75.0 days. The primary grade 3 or 4 toxicities were leukocytopenia (6.7%), pain (14.7%), and nail changes (5.3%). On the basis of this study, it appears that intermittent administration of the docetaxel/estramustine combination might be as effective as continuous administration, but with an improved safety profile; further investigation of this approach is therefore warranted.

**NOVEL THERAPIES FOR HRPC**

Several novel agents are under investigation for the treatment of HRPC [9]. For example, satraplatin, an oral platinum analogue, was recently evaluated in a phase III trial [10]. Initially, 380 patients with HRPC were to be randomly selected to receive satraplatin plus prednisone or prednisone alone, but the trial was discontinued by the sponsor after only 50 patients had been enrolled. However, the European Organization for the Research and Treatment of Cancer followed all patients until progression, and most until death. In an ad hoc analysis of the available data, it appeared that patients who received satraplatin had a significantly greater median progression-free survival than those who did not (5.2 vs 2.5 months; \(P = 0.023\)). The median overall survival was also greater in the satraplatin group, but the difference was not statistically significant (14.9 vs 11.9 months; \(P = 0.579\)). Adverse events were, generally, minimal in both treatment groups. These promising preliminary results have prompted a large phase III trial to evaluate the efficacy and safety of satraplatin plus prednisone vs that of prednisone alone, in patients with HRPC who have previously received one cytotoxic chemotherapy regimen. If the results of this ongoing trial are positive, satraplatin plus prednisone might become an effective second-line therapy for HRPC.

Other novel therapies being evaluated in combination with docetaxel in phase III trials include the vitamin D receptor agonist calcitriol, the endothelin A receptor antagonist atrasentan, and the vascular endothelial growth factor inhibitor bevacizumab. Several types of vaccine are also under investigation in phase III trials. The HER-2/HER-3 inhibitor lapatinib and various modulators of the PI3K/Akt and mTOR signalling pathways are also in development in HRPC. Given the number of promising agents currently under investigation in HRPC, it is likely that new treatment options will be available within 2–3 years.

**CONCLUSION**

In the past 20 years we have learned much about HRPC that has resulted in new approaches to therapy. Although HRPC remains a lethal disease, treatment options are available that can significantly prolong patient survival. First, it is advisable to continue hormone therapy in patients with rising PSA levels despite castrate levels of testosterone, as recommended by the EAU guidelines. Second, many chemotherapy options are now available, with varying degrees of efficacy and tolerability. Docetaxel given every 3 weeks has been shown to prolong survival in patients with metastatic HRPC. Several promising new treatment approaches are in phase III trials in HRPC, and are likely to yield additional therapeutic options for these patients in the near future.

**CONFLICTS OF INTERESTS**

The author has declared no conflicts of interests.

**REFERENCES**


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**Abbreviations:** EAU, European Association of Urology; HRPC, hormone-refractory prostate cancer; SWOG, Southwest Oncology Group.