Treatment options in hormone resistant prostate cancer

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Introduction

Prostate cancer is the most frequently diagnosed cancer in humans. An estimated 189,000 men will be diagnosed with prostate cancer in the USA in 2002, and an estimated 30,200 will die as a result of the disease [1]. It is predominantly diagnosed in older men and is rarely diagnosed in men under the age of 40 in contrast with the observation that microscopic prostate cancer is present in 80–100% of men over the age of 80. The risk of prostate cancer rises steeply with age and continues to increase by 3–4% each year as fewer men are dying from cardiovascular disease. The significance of using prostate-specific antigen (PSA) as a tool to detect prostate cancer has given a boost to early detection and screening. This has led to a different cohort of patients than those who were diagnosed in the pre-PSA era. Before the general use of PSA determinations, relapsing disease was diagnosed based on clinical symptoms such as pain in osseous sites or changes in urination due to local tumour growth, and less frequently, by the presence of visceral disease. Diagnosis was usually made at a later stage and most cases were at a far advanced stage of the disease. In the PSA era, asymptomatic patients are diagnosed as having prostate cancer or disease progression after primary treatment, based on biochemical failure, i.e. rise in PSA [2]. In cases where histological proof of prostate cancer exists, patients will often demand treatment based only on PSA results. It is clear that in cases of localised disease, local treatment by means of surgery or radiotherapy can be curative. When, however, there are signs of locally advanced or metastatic disease, it becomes virtually impossible to cure the majority of these patients. If cure cannot be obtained, a balanced approach weighing toxicity versus efficacy is warranted.

Biological background

The human prostate epithelium is composed of luminal cells with secretory activity, basal cells and dispersed neuroendocrine cells. All cells putatively originate from a stem cell population located in the basal cell layer [3]. After asymmetrical cellular divisions new stem cells are formed and an amplifying cell that has more limited cyclic activity and a shorter, but still significant, life span. These cells will give rise to both end stage exocrine and neuroendocrine cell lineages. Prostate cancer is predominantly composed of cells with a luminal, exocrine phenotype, whereas dispersed cells with neuroendocrine differentiation are regularly present [4]. The representation of basal cells is minimal. A recognisable basal cell layer is not present. The various cells are characterised by the presence of different keratins, K18 for luminal cells, K14 for basal cell, K5 and K14 for amplifying cells, and the neuroendocrine marker chromogranin A (ChA) for neuroendocrine cells.

Multiple genetic changes will lead to independent growth of previously normal cells and ultimately metastatic disease. The precise mechanisms are still poorly understood. The short arm of chromosome 8 and the long arm of chromosomes 13 and 16 (13q and 16q) are the chromosome regions most commonly deleted in prostate tumours. At the time of diagnosis, prostate cancer is clinically considered an androgen-sensitive tumour. Androgen deprivation is therefore the initial treatment of choice in patients with metastatic disease. This deprivation will in most cases lead to tumour regression but ultimately androgen independent progression will occur (median 12–18 months).

These tumours show an increase of intermediate cells, characterised by the lack of K5 expression. Furthermore, accumulation of epidermal growth factor receptor (EGFR) and Bcl-2 is seen [5]. In 30% of the cases with hormone refractory prostate cancer an amplification of the Xq11-q13 locus is found [6]; a region in which the androgen receptor (AR) gene is located. This region is not mutated and contains the wild type AR receptor gene. This overexpression is not found in hormone sensitive tumours. The significance of this finding is unclear. It may reflect adaptation to an androgen deprived state and still reflect normal physiology. The latter is supported by the observation [6] that these tumours may respond to maximal androgen blockade. In 80% of the androgen independent tumours amplifications in the long arm of chromosome 8 (8q) have been found. A third gene also relevant in this setting is cIIF3-p40, which is overexpressed in 30% of androgen independent tumours [5]. Other regions of interest are 7q, 7p and 18q. Relevant genes on chromosome 7 are EGFR, MDRI and CAV1.
Treatment options for hormone refractory prostate cancer (HRPC)

In view of the increased insight in the biology of cancer, and more specifically of prostate cancer, there are many options which can be considered in patients who develop HRPC. Potential approaches are secondary hormonal manipulations, immunotherapy, chemotherapy, inhibition of invasion and metastases, inhibition and or blockade of growth factor receptors or growth factor receptor pathways and inhibition of neo-angiogenesis.

A few general comments should be made before discussing the results of chemotherapy and other approaches. The patient population enrolled in these studies can be very heterogeneous with respect to prior therapy and extent of disease. How many lines of hormonal therapy have been given? What was the extent of radiotherapy given? The latter is especially relevant in view of bone marrow reserve, quite often a relevant factor for adequate chemotherapy. Is it a PSA relapse or clinically symptomatic disease? Furthermore, when chemotherapy is given, is continuous hormonal treatment required? Sufficient information regarding the degree of androgen deprivation is not always given. What is the definition of hormone refractory disease? Androgen independent is not the same as hormonal independent. Patients who progress after androgen ablation may respond to ketoconazole [7], corticosteroids [8], aminoglutethimide [9], anti-androgens, such as flutamide [10], estrogens [11], estramustine phosphate [12] and progestational agents [13]. Furthermore, responses after withdrawal of anti-androgens in the presence of castrate levels of testosterone are well documented [14]. This type of information is quite often not given.

Minimal requirements for entry into protocol or for changing therapy in a patient who becomes refractory to treatment include (i) castrate levels of serum testosterone and (ii) clinical or biochemical evidence of disease progression. In the case of anti-androgens, documentation of progression after withdrawal for a minimum of 4–6 weeks prior to the start of new therapies is required. Endpoints of clinical studies can be objective response with measurable disease, decline in PSA levels, quality of life, pain relief or change in analgesic use or both, time to progression, time to new therapies and, most important, overall survival.

These heterogeneous endpoints make it difficult to discuss the results of various trials. Response in bone, the most frequent site of metastatic disease, is very difficult to measure. Therefore, the objective results observed in patients with soft tissue, measurable disease may not reflect the disease that is most generally seen in the population.

Changes in PSA generally correlate with the activity of prostate cancer in all stages. Most patients with relapsing disease have elevated PSA levels [15]. Prostate-specific antigen rise as a surrogate endpoint for disease progression has been subject to misinterpretation, given the fact that PSA rise precedes radiographic and clinical progression by a matter of months or even longer [16]. It is however recognised that PSA levels can change as a function of hormonal status or by chemotherapy itself, independent of the degree of cell kill [17]. It is also recognised that tumours consist of PSA-producing and non-producing cells. Cell lysis of non-producers will not be reflected in PSA changes and vice versa. Last, but not least, what exactly is a PSA response? Again endpoints have been interpreted differently by different authors, e.g. a 50% reduction from baseline, an 80% reduction [18]?

To assess to what degree PSA decline correlates with survival in hormone refractory disease, a retrospective multivariate analysis was undertaken. The results indicated that a PSA decline of 50% or more correlated significantly with survival [19]. These results were confirmed in an independent study from the Norwegian Radium Hospital [20]. These factors must be considered when evaluating the results of various studies and approaches. Recently, guidelines have been published to address this problem. Four groups were discerned: 1. progressive measurable disease; 2. progressive bone metastasis; 3. stable metastases and rising PSA and 4, rising PSA without evidence of disease. Prostate-specific antigen endpoint should be reported as a 50% decline, confirmed by a second measurement 4 weeks later without radiological disease progression. Response duration and time to PSA progression may also be an important clinical endpoint [21].

Chemotherapy

No intervention with chemotherapy has been demonstrated to improve survival in a randomised controlled trial in patients with relapsed disease. In early studies with measurable disease as an endpoint, cytotoxic chemotherapy was considered inactive [22–24] (Tables 1 and 2).

Using other endpoints, a few randomised studies have shown an advantage for chemotherapy. In two of these randomised studies mitoxantrone plus corticosteroids were compared with corticosteroids alone [25, 26]. Mitoxantrone is an anthracycline with a milder toxicity profile than doxorubicin. In the study performed by Tannock et al. [25], 161 symptomatic patients were randomised between mitoxantrone 12 mg/m² plus prednisone 10 mg versus prednisone alone. Non-responders to prednisone were allowed to cross over. Symptom relief measured on a pain scale was the primary endpoint next to duration of palliative response, PSA response, quality of life and overall survival. Regarding the primary endpoint of pain and analgesic use, there was a significant advantage (29% versus 12%) in favour of the combination. There was no difference in PSA response or survival. A second study [26] described the results in 242 patients randomised between mitoxantrone 14 mg/m² plus hydrocortisone 40 mg daily versus hydrocortisone alone. In this study, survival was the primary endpoint with progression-free survival, PSA response, measurable response and quality of life as secondary endpoints. The median survival was
similar (12.3 versus 12.6 months) and did not reflect the difference in progression-free survival (3.7 versus 2.3 months, \( P = 0.025 \)). Similar to the previous study, there was an improvement in quality of life and observed toxicity was low. In this study a decline in PSA of 50% and 80% paralleled an improvement in survival of 20.5 versus 10.3 months, underlining the potential use of PSA decline as a surrogate endpoint for survival.

Another agent frequently used either alone or in combination with cytotoxic agents is estramustine, a conjugate of nitrogen mustard and estradiol. As monotherapy only modest activity has been found (14% PSA response). When Estracyt™ was combined with vinblastine in three separate phase II trials, cumulative data revealed a >50% decrease in PSA in 46–61% of patients, with measurable disease regression in 24% [27–29]. Two phase III randomised studies of the combination have been performed. A study in the USA compared vinblastine 4 mg/m² weekly versus vinblastine plus estramustine 600 mg/m²/day for 6 weeks [30]. In this study, 201 patients were included. No difference was found in the primary endpoint (survival 9.2 versus 11.9 months). Estramustine plus vinblastine had a small but significant advantage in progression-free survival compared with vinblastine alone (3.7 versus 2.2 months; \( P < 0.001 \)). Sustained PSA responses of ≥3 months were more common in the arm that included estramustine, which was not surprising, given the hormonal component of the drug (25.2 versus 3.2%; \( P < 0.0001 \)). Although gastrointestinal toxicity was worse with the addition of estramustine, there was significantly less granulocytopenia in the combination arm. In contrast, a second European Organisation for Research and Treatment of Cancer (EORTC) study compared the combination of estramustine and vinblastine to estramustine alone. This study was discontinued due to toxicity and found no overall differences between the two arms [31].

Taxanes are among the most active class of drugs tested so far in combination with estramustine in phase II trials. Initial trials of paclitaxel alone suggested no significant activity, but when combined with estramustine, a PSA response rate of 65% was reported, with measurable responses in 57% of cases [32]. Another phase II trial of estramustine, weekly paclitaxel, and monthly carboplatin showed PSA responses in 19 of 26 (73%) patients lasting a median duration of 6+ months with short follow-up. Measurable responses were seen in nine of 14 patients (64%) [33].

In a phase I study, 34 patients treated with docetaxel and estramustine experienced PSA declines of ≥50% in 63% (95% CI 28% to 81%) and objective partial responses in five of 18 men with measurable disease. The recommended phase II dose of docetaxel was 70 mg/m² every 3 weeks in minimally pretreated patients and 60 mg/m² in extensively pre-treated patients when combined with estramustine 280 mg t.i.d. for 5 days [34].

Kreis et al. [35] reported the maximal tolerated dose (MTD) of docetaxel to be 70 mg/m² every 3 weeks when given in combination with estramustine 14 mg/kg/day. PSA responses were seen in 14 of 17 patients. Dose-limiting toxicities were grade 4 leukopenia and grade 3 fatigue and diarrhoea. Cancer

### Table 1. Randomised studies in hormone refractory prostate cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>n</th>
<th>Response</th>
<th>Impact on PFS/OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tannock</td>
<td>Prednisone (10 mg/day) versus mitoxantrone plus prednisone</td>
<td>161</td>
<td>Significant symptomatic improvement</td>
<td>–/–</td>
<td>25</td>
</tr>
<tr>
<td>Kantoff</td>
<td>Hydrocortisone (40 mg/day) versus mitoxantrone plus hydrocortisone</td>
<td>242</td>
<td>Significant symptomatic improvement</td>
<td>–/–</td>
<td>26</td>
</tr>
<tr>
<td>Hudes</td>
<td>Vinblastine versus vinblastine plus EMP (600 mg/m²)</td>
<td>201</td>
<td>PSA response 3.2% versus 25.2%</td>
<td>/– (trend). Time to progression 2.2 versus 3.7 months (( P &lt; 0.001 ))</td>
<td>30</td>
</tr>
<tr>
<td>Berry</td>
<td>Paclitaxel versus paclitaxel plus EMP (280 mg)</td>
<td>166</td>
<td>PSA response 25% versus 48%</td>
<td>12 months PFS 8% versus 29% (( P = 0.08 ))</td>
<td>42</td>
</tr>
<tr>
<td>Small</td>
<td>Suramin plus hydrocortisone versus placebo plus hydrocortisone</td>
<td>460</td>
<td>Significant symptomatic improvement. PSA response 33% versus 16%</td>
<td>+/-</td>
<td>63</td>
</tr>
</tbody>
</table>

EMP, estramustine phosphate; OS, overall survival; PSA, prostate-specific antigen; PFS, progression-free survival.

### Table 2. Phase II combination studies in hormone resistant prostate cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Drugs</th>
<th>n</th>
<th>PSA response (%)</th>
<th>WHO response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudes</td>
<td>Paclitaxel 96 h ci plus EMP</td>
<td>35</td>
<td>53</td>
<td>44% (4/9)</td>
<td>32</td>
</tr>
<tr>
<td>Kelly</td>
<td>Paclitaxel/carboplatin/EMP</td>
<td>26</td>
<td>73</td>
<td>64% (9/14)</td>
<td>33</td>
</tr>
<tr>
<td>Petrylak</td>
<td>Docetaxel/EMP</td>
<td>34</td>
<td>63</td>
<td>28% (5/18)</td>
<td>34</td>
</tr>
<tr>
<td>Savarese</td>
<td>Docetaxel/EMP/hydrocortisone</td>
<td>46</td>
<td>68</td>
<td>50% (12/24)</td>
<td>36</td>
</tr>
</tbody>
</table>

EMP, estramustine phosphate; ci, continuous infusion.
and Leukaemia Group B (CALGB) completed a phase II study of docetaxel, estramustine and low-dose hydrocortisone in 47 men with hormone refractory prostate cancer, of whom 40 were evaluable for response. Sixty-nine per cent had a PSA response and 23% with measurable disease had a partial or complete response [36].

Studies of estramustine and docetaxel indicate PSA responses in the range of 39–82%, objective responses in ~25%, improvement in Karnofsky performance status or pain symptom control in the range of 53–88% [34–37].

Survival data are usually not reported, with the exception of one phase I trial in which a median survival of 22.8 months was observed [34]. The safety profile of the combination is acceptable.

More recently, efforts have focused upon optimizing the schedule of paclitaxel and docetaxel by using lower doses of estramustine and weekly taxanes [38–41]. In an ECOG study, Estracyt 280 mg/m² b.i.d. on the day before, day of and day after taxol 90 mg/m² weekly was given to 63 metastatic HRPC patients. They showed that this regimen was active and less toxic than other taxane–Estracyt combinations [41].

In a randomised trial of 166 patients treated with weekly paclitaxel and estramustine versus paclitaxel alone, the response rate with the combination was better than with the single agent (48% versus 25%) [42]. These data are of interest and require further confirmation.

In this context, an international industry sponsored trial will randomise 804 patients with HRPC between mitoxantrone and prednisone or docetaxel and prednisone. Docetaxel will be given either every 3 weeks or on a weekly schedule. The primary end point is survival, while the secondary end points are response rate and quality of life. Another randomised trial by the South West Oncology Group (SWOG) is focusing upon the combination of estramustine and docetaxel compared with mitoxantrone and prednisone in 620 patients. The results of this study should be of very great interest as many investigators continue to study taxanes in phase II trials and are really unsure as to which combination will be better.

Other estramustine drug combinations, including with vinorelbe and etoposide, have similar levels of activity [43]. Raghavan et al. [44] administered oral cyclophosphamide at a dose of 100 mg/m² for 14 days every 28 days to 30 patients with HRPC. Eighteen (60%) had a significant improvement in symptoms, whereas six (20%) had objective partial responses (PRs). Toxicity was mild including nausea, fatigue and anae-mia. Combinations of estramustine, etoposide and paclitaxel have also been reported to have high response rates [45].

For patients with HRPC, prognostic indicators can be important [46]. The most relevant factors are performance status, haemoglobin levels, weight loss, lactate dehydrogenase (LDH) and on treatment a PSA decline of ≥50%. As previously indicated, no survival advantage has been found for any of these combinations and careful weighing up of toxicity versus efficacy is essential.

**Immunotherapy**

Immunotherapy with Bacillus Calmette-Guerin is an established approach for superficial bladder cancer, especially for carcinoma *in situ*. It has a role in the treatment of renal cell carcinoma and melanoma, but in other forms of cancer its significance is unclear. In prostate cancer its role has also been explored [47, 48].

One approach is the use of dendritic cells (DC) to enable adequate antigen presentation to induce specific T-cell responses and to activate B-cells to trigger antibody formation. Dendritic cells can be generated *in vitro* from peripheral blood monocytes with the use of granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin-4. In a phase I trial [49], DC were loaded with prostate-specific membrane antigen (PSMA) and administered by intravenous infusion. Partial response was defined as a 50% reduction in PSA level or by improvement on ProstaScint scan. In seven of 51 patients a PR was seen and 11 patients had stable disease. In a second series, 37 patients were treated with six peptide pulsed DC infusions at 6 weekly intervals. In one patient a complete response and in 10 patients a PR was observed [50].

Another approach to vaccination is the use of GM-CSF transfected autologous irradiated tumour cells [51]. In seven of eight patients a positive DTH response was seen (2/8 positive prior to vaccination) and in the sera of these patients antibodies were detected that recognised polypeptides from prostate cells. The toxicity of these approaches is negligible. No randomised data are available. Although the techniques required are complicated and quite laborious, there may be a role for these types of treatment modalities.

Small et al. [52] gave systemic GM-CSF to 36 patients with progressive disease after androgen deprivation and antiandro-gen withdrawal. Differences in the PSA doubling time and slope were noted. Changes in PSA could not be easily attributed to direct or indirect effects of GM-CSF on the PSA assay or down-regulation of PSA expression by GM-CSF. Toxicity was very mild, consisting primarily of transient constitutional symptoms and injection site reactions. These data suggest that GM-CSF may have antitumour activity in advanced prostate cancer, and that the use of GM-CSF may be a confounding variable when PSA responses are used as an end point in clinical trials.

In another phase II trial in less heavily pre-treated patients, Dreicer et al. [53] also reported PSA responses. This led to a more recent trial combining GM-CSF 350 mg three times per week with thalidomide 100–200 mg/day, an anti-angiogenic agent in patients with HRPC.

**Inhibition of angiogenesis**

It is well recognised that tumour cells require neo-angiogenesis for their growth and metastatic spread [54]. Neo-angiogenesis is induced by hypoxia and various tumour-related factors. Some of the most relevant stimulating factors
that have been identified so far are vascular endothelial growth factor (VEGF), basic and acidic fibroblast growth factors (α- and β-FGF), and tumour growth factor β (TGF-β). Blockade of receptors or downstream pathways are means to impair malignant growth and spread. Anti-angiogenic therapy is expected to be mainly cytostatic rather than cytotoxic and prolonged intake is thought to be essential. Factors evaluated so far include natural antagonists to angiogenesis such as the natural antagonists endostatin, thrombospondin and angiostatin, synthetic analogues, receptor antibodies and small molecule receptor inhibitors.

In prostate cancer increased vascularisation has been associated with an aggressive phenotype [54] and increased plasma levels of VEGF have been found during tumour progression [55]. Prostate cancer is an interesting target for this form of therapy. Although many abstracts have been published, no finalised papers have thus far been available to shed definitive insight into their role in this disease.

Growth factor receptor inhibition

Growth factor receptor inhibition may turn off the cell cycle stimulating cascade in various cancer types depending upon its role and state of activation. This inhibition can be achieved either by blockade of the receptor using monoclonal antibodies or by inhibitors of protein kinases, receptor kinases and farnesyl transferase.

The epidermal growth factor receptor Her-2/neu is expressed in normal prostate epithelial cells and is overexpressed in a subset of human prostate cancers [56]. In a recent study, trastuzumab (Herceptin) and paclitaxel were evaluated in androgen dependent and androgen independent prostate carcinoma (AIPC) [56]. Patients were stratified for androgen dependency and the presence of HER-2. Treatment consisted of weekly trastuzumab at a dose of 2 mg/kg (after a 2 mg/kg loading dose) until disease progression, when weekly paclitaxel was added at 100 mg/m². In total, 130 patients were screened for HER-2 expression and 23 treated. All patients experienced disease progression on trastuzumab alone. Fifteen patients were treated with the combination, only three patients showed a PSA response (>50% decline). Her-2 expression was only found in metastatic tissue of AIPC. Based upon the prior experience in breast cancer [57], it seems essential to have this receptor information prior to the start of experimental therapy. Trastuzumab was ineffective in HER-2 negative tumours.

Inhibition of the epidermal growth factor receptor (EGFR) by monoclonal antibodies or small molecule tyrosine kinase inhibitors may be another interesting strategy in the treatment of prostate cancer [58].

Another growth factor receptor to be targeted in this disease is the insulin-like growth factor receptor [59]. No clinical data are yet available.

Suramin is polysulfonated naphthylurea and has been shown to block the binding of a wide range of peptide growth factors including platelet derived growth factor, TGF-α, EGF, TGF-β, bFGF and IGF [60]. Other mechanisms include inhibition of adrenal gland function, protein kinase C, and topoisomerase II. Initial studies were promising [61]. To date, only one placebo-controlled randomised study with pain relief and use of analgesics as surrogate endpoint has been published [62]. Suramin was given i.v. as a loading dose of 1000 mg/m² on day 1 followed by 400, 300, 250 and 200 mg/m² on days 2–5, and thereafter 275 mg/m² twice weekly for 2 weeks and followed once weekly until week 12. This was combined with hydrocortisone 40 mg daily. In total, 460 patients were entered and there was a significant reduction in pain and analgesic intake in the combination arm. The duration of response was longer (240 versus 69 days) and the proportion of patients with a >50% PSA decline was higher (33% versus 16%). Quality of life and performance status were not compromised by suramin. Overall survival was similar. With the exception of rash the two arms had a similar profile of adverse events.

Other approaches

This overview cannot possibly cover all potential new treatment modalities which are currently under development. A few remarks can be made.

Antisense therapy is an interesting strategy that may be of interest. Bcl-2 appears to have a role in the transition from androgen-dependent to androgen-independent growth. Bcl-2 functions to prevent programmed cell death. There is increasing evidence that Bcl-2 protein confers a multidrug resistance phenotype that encompasses many classes of cytotoxic chemotherapy agents. Antisense therapy with Genasense™ (Bcl-2 antisense oligonucleotide therapy) consists of modified stretches of single-stranded DNA complimentary to mRNA regions of a target gene. This represents a strategy to target functionally relevant genes. Genasense™ appears to be active in prostate cancer cell lines and xenograft models and is synergistic with docetaxel in xenografts. In addition, it appears that docetaxel may function to overcome the multidrug resistance phenotype by inhibiting Bcl-2 dimerisation with BAX protein and thus promoting programmed cell death. Genasense has been given in combination with both mitoxatrone and with taxotere in preliminary phase I/II studies [63–65].

Gene therapy is a potential means of correcting aberrant cell cycle regulation in tumour cells or by introducing genes which may, independent of the underlying genetic defect, destroy the cancer cell. In view of the fact that prostate cancer is formed as a consequence of at least five cumulative genetic changes, it will be difficult to correct these mutations with gene therapy. Furthermore, the application of this treatment is confounded by the fact that the current vector technology does not give a stable integration of genes into 100% of the cancer cells.
in vivo [66]. In pre-clinical in vitro and in vivo models encouraging results have been achieved [67]. Attempts at restoration of normal gene function include insertion of suppressor genes, such as p53, Rb, p21 and p16, and attempts to counteract the effects of tumour promoting oncogenes such as ras, myc, erbB2 and bcl-2 [66]. The major challenge for the near future is to find a means of improving the delivery of genes both locally and systemically. Furthermore, combinations with other modalities should be developed.

Conclusions

Hormone independent prostate cancer reflects a heterogeneous patient population. Formerly the main category consisted of symptomatic patients with far advanced disease and quite often compromised biological functions (bone marrow reserve) and performance status. To date, due to intensive PSA guided follow-up, patients can be hormone refractory without the presence of extensive macroscopic disease. The knowledge that the tumour has escaped hormonal control is disturbing to most patients and further therapies are usually requested. To date, there is no systemic therapy available that has been proven to prolong overall survival. Intermediate or surrogate end points in this disease include palliation of debilitating symptoms, most frequently due to bone disease. A few combinations have been shown to induce significant clinical improvement over corticosteroids alone. In view of the toxicity pattern and ease of administration, the combination of prednisone and mitoxantrone has become an acceptable treatment for symptomatic patients. New chemotherapeutic approaches, especially taxane-based combinations are under investigation. Combinations with estramustine seem interesting in this respect. Prognostic factors reflecting different patient categories should be regarded. Combinations with other therapies such as receptor blockers, angiogenesis inhibitors, gene and immunotherapy are probably needed to make the next step. Easy solutions are not available. Next to tumour directed therapies, optimal supportive care and watchful waiting are valid strategies in this disease.

References

25. Tannock IF, Osoba D, Stockler MR et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic


40. Leitner SP, Scoppettuolo M, Kanowitz JM et al. Phase II trial of weekly one hour paclitaxel (T) plus oral estramustine (E) taken the day before, of, and after paclitaxel in patients (pts) with metastatic hormone refractory prostate cancer (HRPC). Proc Am Soc Clin Oncol 1999; 18: 345a (Abstr 1331).


