PERGAMON

European Journal of Cancer 39 (2003) 136–146

European Journal of Cancer

www.ejconline.com

Current Perspective

What's new in the treatment of advanced prostate cancer?

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Received 26 September 2002; received in revised form 27 September 2002; accepted 30 September 2002

Abstract

Increased insight into the biology of prostate cancer and the emergence of new therapeutic strategies and chemotherapeutic agents has changed approaches in treating patients with advanced prostate cancer. After secondary hormonal manipulations, new approaches include: second-line hormonal therapy, chemotherapy, immunotherapy with granulocyte macrophage-colony stimulating factor (GM-CSF) therapy, dendritic cell therapy, gene vaccination therapy, inhibition and/or blockade of growth factor receptors or growth factor receptor pathways, inhibition of neo-angiogenesis and inhibition of invasion and metastases.

Keywords: Prostate cancer; Treatment; Hormone-refractory; Second-line; Immunotherapy; Chemotherapy; Gene therapy; New agents

1. Introduction

Increased insight into the biology of prostate cancer and the emergence of new therapeutic strategies and chemotherapeutic agents has altered the nihilist approach that had often been adopted for patients with advanced prostate cancer. Hormone-refractory prostate cancer (HRPC) demonstrates resistance to many chemotherapeutic agents that are diverse both in structure and mechanism of action. Chemotherapy has demonstrated limited durable antitumour activity, and no demonstrable survival benefit in randomised studies [1].

HRPC reflects a heterogeneous patient population. Formerly, HRPC consisted of symptomatic patients with very advanced disease, compromised bone marrow reserve and poor performance status. Now, due to intensive prostate-specific antigen (PSA)-guided follow-up, patients may have HRPC without having extensive macroscopic disease. The knowledge that tumour has escaped preliminary hormonal control (rising PSA), is disturbing to most patients and further therapies are usually requested.

HRPC refers to progressive disease despite castration serum levels of testosterone. The development of hormonal resistance predictably occurs after androgen deprivation. The median time to progression is 18 months. Median survival in older studies was approximately 6 months [2]. Due to stage migration, these numbers are no longer entirely realistic and different categories of patients must be taken into account in the planning of studies and in the interpretation of the results of trials in HRPC. Investigators have questioned the use of this terminology, as many patients are not truly 'hormone-refractory'.

For this reason, baseline quality of life measurements may help to select subsets of patients according to prognosis. Using data from three European Organization for Research and Treatment of Cancer (EORTC) studies in HRPC, patients were classified into three categories. Patients with a good prognosis had a median survival of 18.7 months, intermediate prognosis patients had a median survival of 11.9 months, and poor prognosis patients had a median survival of 6 months. 29% of the patients were in the good prognosis category [3].

In addition, interpretation of trials in advanced prostate cancer has been confounded by the lack of measurable disease. Intermediate or surrogate endpoints for evaluating new therapies in clinical trials have included: PSA, quality of life and palliation of symptoms. Furthermore, interpretation of PSA after therapy may be complicated because a drug may decrease PSA release

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0959-8049/03/$ - see front matter
PII: S0959-8049(02)00665-2

without killing a cell. PSA expression is modulated by a number of agents, including androgens, retinoids and vitamin D, as well as growth factors. This can be overcome by requiring that a given degree of decline is documented more than once, and be maintained for a defined period of time before classifying a patient as having a 'benefit'. For instance, after *cis*-retinoic acid or other differentiating agents, an increase in PSA may precede a decline [4].

2. Newer hormonal manipulations

The gonadotropin-releasing hormone (GnRH) antagonists are a new therapeutic class of agents that directly block pituitary gonadotropin-releasing hormone receptors. This monotherapy, administered in a monthly depot formulation, immediately reduces testosterone to castration levels. Two phase II trials and three phase III trials have been conducted with Abarelix both in Europe and in the USA [5–10].

These antagonists produce a rapid decrease in prostate volume and in PSA, without a testosterone surge and swift testosterone recovery upon suspension. A 3-monthly preparation of luteinising hormone-releasing hormone (LHRH)-antagonists is not yet available, so one must weigh the potential advantages of this kind of therapy against the expense and tolerability.

There is also some interest in developing selective androgen receptor modulators (SARMs) that can achieve androgen receptor (AR) blockade without causing the increased testosterone levels produced by the non-steroidal anti-androgens currently in use [11].

After hormonal manipulations, new approaches include: second-line hormonal therapy, chemotherapy, gene therapy, immunotherapy, inhibition and/or blockade of growth factor receptors or growth factor receptor pathways, inhibition of invasion and metastases and inhibition of neo-angiogenesis.

3. Second-line hormonal therapy

Second-line hormonal treatment diminishes circulating adrenal androgens. This may cause tumour regression by suppressing any remaining hormone-dependent prostatic cancer cells, but may also occur due to mechanisms other than adrenal suppression. A variety of hormonal therapies, such as flutamide, have been used as second-line therapy with modest results that have been well documented [12]. Following disease progression, remaining androgen sensitive cells may respond to second-line hormonal therapy.

One of the most important observations is the "flutamide withdrawal syndrome" [13]. Up to 40% of patients failing CAB will respond when the antiandrogen is discontinued. Long-term androgen ablation with antiandrogens may lead to increased expression and activity and mutation of the androgen receptors in some 50% of patients [14]. This may explain why discontinuation of the anti-androgen may lead to a decrease in PSA.

Ketoconazole is an oral imidazole derivative with antifungal properties that works through a hormonal–adrenal mechanism and by inhibiting the cytochrome p-450 enzyme system. Ketoconazole may act by modulation of retinoic acid breakdown. In combination with hydrocortisone, a $>50\%$ decline in PSA in 30 (63%) patients was reported for a median duration of 3.5 months. Toxicities included mild Grade 1 or 2 nausea, fatigue, oedema, hepatotoxicity and rash in 4–10% of patients [15]. As part of a larger Cancer and Leukemia Group B (CALGB) study, 260 patients were treated with antiandrogen withdrawal followed by ketoconazole and hydrocortisone at progression. The PSA response to anti-androgen withdrawal in this large multicentre study was modest; 13%. Response to antiandrogen withdrawal and ketoconazole was higher, 27%. There was no difference in survival with early versus delayed used of ketoconazole [16]. A regimen of low-dose ketoconazole (200 mg three times per day) has been recently shown to be effective [17].

4. Chemotherapy

No chemotherapeutic agent or regimen has thus far been able to demonstrate an improvement in survival in patients with HRPC [1]. Using quality of life endpoints, two randomised studies have shown an advantage for the combination of mitoxantrone and a corticosteroid compared with corticosteroids alone [18,19].

Encouraging data have also been reported with the taxanes. Both paclitaxel (Taxol) and docetaxel (Taxotere) work by promoting microtubular assembly and by inhibiting disassembly [20–22]. Based on the assumption that agents that inhibit microtubules may work well together, the combination of Estracyt and either paclitaxel or docetaxel have been evaluated in varying schedules. Estracyt, the combination of oestradiol + nornitrogen mustard, is synergistic with vinca alkaloids, VP-16 and the taxanes. Estracyt bypasses the multidrug resistance (mdr) phenotype and has non-overlapping toxicity (primarily gastrointestinal) with other cytotoxic agents.

The combination of Estracyt plus a 96-h infusion of paclitaxel produced a 50% decrease in PSA in 17 of 32 (53%) patients. The median time to progression, based on increasing PSA level and other clinical criteria, was 22.5 weeks. The estimated median overall survival time was 69 weeks [23].

In a randomised study, weekly paclitaxel plus Estracyt 280 mg orally three times a day on the day before therapy,

the day of treatment and the day after paclitaxel was compared with weekly paclitaxel alone. There was a difference in favour of the combination with a 48% response rate (RR) for the combination versus 25% with paclitaxel alone, with progression-free survival at 12 months of 29% versus 8%. Median survival was 15.1 months compared with 12.9 months [24]. Unfortunately, this study was too underpowered to make definitive conclusions.

Most recent efforts have been focused upon the optimal schedule of paclitaxel or docetaxel with lower does of Estracyt. For this reason, there is interest in the weekly administration of taxanes [22,25,26]. Preliminary data have been extremely promising and requires further exploration.

Docetaxel was evaluated in two phase II studies. A 50% decrease in PSA in 42–45%, with objective response rates described in a smaller population of patients with measurable disease in 28–42% was observed [21,27]. In addition, several phase II trials of weekly docetaxel have demonstrated similar PSA responses of 34–60% [25,28,29]. Survival data are usually not reported with the exception of one phase I trial in which a median survival rate of 22.8 months was observed in patients mostly previously treated with prior chemotherapy [30]. The safety profile of the combination appeared acceptable.

These results appear similar to the every 3-week schedule, with perhaps somewhat less haematological and neurological toxicity. However, more corticosteroids are administered and may be associated with more fluid retention. An international industry sponsored trial will randomise 804 patients with HRPC between mitoxantrone and prednisone versus docetaxel weekly or every 3 weeks (three arms).

Meanwhile, the Southwest Oncology Group (SWOG) has initiated a similar phase III trial comparing Estracyt and docetaxel with mitoxantrone and prednisone in 620 patients with HRPC. The results of these two studies are of extreme interest as many investigators continue to study the taxanes in phase II trials and are really unsure as to which combination is best.

Other new agents act upon different phases of the cell cycle. The epothilones are semi-synthetic analogues of natural epothilones B and D which have a mode of action similar to the taxanes (microtubular stabilisation). They have activity in both paclitaxel-sensitive and refractory tumours, and are twice as potent as paclitaxel in inducing tubulin polymerisation *in vitro*. Cytotoxicity is mediated through induction of Bax conformational changes [31]. Phase I trials have already shown activity in HRPC. The epothilone B analogue BMS-247550 combined with estramustine demonstrated responses in 11 of the first 12 patients treated [32].

Other new taxanes in clinical trials include: BMS 184476, BMS 188797, BMS 275183, IDN 5109/BAY 598862, RPR 109881A and RPR 116258. These new agents have a common characteristic, decreased recognition by p-170, the product of the MDR1 gene. This confers innovative properties such as *in vitro* and *in vivo* activities on tumours expressing the p-170, and the advantage of oral administration [33].

5. Immunotherapy

Until recently, prostate cancer was considered to be a non-immunogenic tumour. This paradigm has changed and the role of immunotherapy has been explored [34,35]. Immunomodulatory cytokines and dendritic cell therapy show promising results.

One approach is the use of granulocyte macrophage-colony stimulating factor (GM-CSF) either alone or in combination. GM-CSF stimulates production of the anti-angiogenesis protein plasminogen activity inhibitor type 2 (PAI 2). Small and colleagues gave systemic GM-CSF to 36 patients with progressive disease after androgen deprivation and anti-androgen withdrawal [36]. The first cohort ($n=22$) received GM-CSF at 250 $\mu g/m^2$ subcutaneously (s.c.) days 1–14, every 28 days. The second group ($n=13$) received an initial daily 2-week course followed by therapy given 3 days/week. Responses were seen in both cohorts including 1 patient who had a $>99\%$ decrease in PSA associated with an improvement in bone scan for 14+ months. Differences in the PSA doubling time and slope were noted in both arms. 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.

In another phase II trial, in less heavily pretreated patients (both hormone-naïve and -independent), Dreicer and colleagues reported PSA responses with GM-CSF given at dose of 250 $\mu g/m^2$ three times per week [37]. This led to a more recent trial combining GM-CSF 250 $\mu g/m^2$ three times per week with thalidomide 100–200 mg/day, an anti-angiogenic agent, in patients with HRPC [38]. The initial dose of thalidomide has been revised to a 2-week wash in schedule. PSA and measurable response have been documented. Most likely this therapy should be used in patients with less tumour burden.

6. Gene therapy

Gene therapy is a potential means to correct aberrant cell cycle regulation in tumour cells by introducing genes which may lead to a therapeutic benefit. In view of the

fact that prostate cancer is formed as a consequence of at least five cumulative genetic changes, it is not that easy to correct these mutations with gene therapy. Application of this treatment is also confounded because current vector technology does not give a stable integration of genes into 100% of the cancer cells *in vivo* [39]. Nonetheless, in preclinical *in vitro* and *in vivo* models encouraging results have been achieved [40].

Many trials of gene therapy, the use of genetic materials (DNA or RNA), have been initiated in prostate cancer. Strategies for gene therapy include vaccine therapy with various cytokines such as interleukin2 (IL-2) or GM-CSF and suicide cytotoxic therapy such as herpes simplex virus (HSV)-thymidine kinase or toxins. This includes attempts at restoration of normal gene function by insertion of suppressor genes such as *p53* or *Rb*, *p21* and *p16*, and attempts to counteract the effects of tumour promoting oncogenes such as *ras*, *myc*, *erbB2* and *bcl-2*. Gene therapy has encompassed oncolytic viruses specifically designed to replicate preferentially in prostate cancer cells (CV787 or CN-706) and anti-sense therapy against bcl-2 and C-myc [41–43].

The first autologous gene therapy phase I trial of GM-CSF vaccination was an *ex vivo* trial performed at the Johns Hopkins Center. Both T cell and B cell immune responses to human prostate cancer were generated by treatment with GM-CSF-transfected autologous irradiated tumour cells [44]. In 7/8 patients, a positive DTH response was seen (2/8 positive prior to vaccination) and in the sera of these patients antibodies were detected recognising polypeptides from prostate cells. Toxicity was negligible. Since then, a number of phase II trials have been initiated. No randomised data are available. Although the technical requirements are quite complicated, there may be a role for these types of treatment modalities.

7. Dendritic cell vaccination therapy

Dendritic cells (DC) are the only cells in the body that stimulate naive T cells, and can activate B-cells to trigger antibody formation. DC can be isolated by leucophoresis of monocyte precursors and acquire the form of mature DC after culture with cytokines such as GM-CSF and IL-4. DC are bone-marrow derived leucocytes that lack cell surface markers for B,T, Natural Killer (NK) or monocyte, and macrophage lineage cells [45,46]. These cultured cells exhibit the features of antigen presenting cells, stimulating both CD4 and CD8 T-cell subsets. The premise is that DC can be isolated from patients, loaded with tumour antigens, and used to induce a specific antitumour response [47].

In a phase I trial [48], DC were loaded with prostate-specific membrane antigen (PSMA) and administered by intravenous (i.v.) infusion. Partial response (PR) was defined as a 50% reduction in PSA level or by improvement on ProstaScint scan. In 7 of 51 (14%) patients, a PR was seen and 11 patients had stable disease. In a second study, 37 patients were treated with 6-weekly peptide pulsed DC infusions. One patient had a complete response (CR) and 10 achieved a PR [49].

DC therapy APC-8015 (Provenge) is under development [50]. Autologous blood antigen presenting cells (APC), primarily DC, are harvested and pulsed with prostatic acid phosphatase (PAP)-sargramostim (GM-CSF) fusion protein to produce Provenge. Phase I/II trials in HRPC show that Provenge is safe, induces clinical response, and may prolong the time to disease progression (TTP). Development of immunity to PAP has been associated with an improved TTP [51].

In a phase III trial, 127 patients were randomised (2:1) ratio to i.v. Provenge or placebo (unactivated APC). Placebo patients received Provenge at the time of progression. Provenge was safe and well tolerated and induced antigen-specific immunity [52]. In another trial, patients received a combination of Provenge and bevacizumab (antivascular endothelial growth factor; anti-VEGF monoclonal antibody). Treatments were repeated every 14 days for three courses. Patients continued to receive bevacizumab alone every 14 days in the absence of disease progression or unacceptable toxicity [53].

Meanwhile, at Duke University, patients have been given escalating doses of PSA mRNA-transfected DC with no evidence of dose-limiting toxicity or adverse effects, including autoimmunity [54].

8. *In vivo* gene therapy

In vivo gene therapy is more cost efficient and does not have to be tailored to the individual patient. Disadvantages are that gene transfer efficiency is poor and stimulation of host immunity may have untoward toxicity. There are many methods for DNA gene transfer including viral, liposomal and other novel methods. Adenoviral and retroviral methodology have been the major focus of attention [55].

Development of genetically engineered conditionally replication competent adenoviruses via prostate-specific promoters has led to trials of CN706 (prostate-specific oncolytic virus) [42] and to a preliminary phase I/II dose-finding trial with CV787, another prostate cancer-specific adenovirus [41]. In addition, CV787-mediated replication-dependent cytotoxicity seems to be synergistic with both paclitaxel and docetaxel chemotherapy [56].

Yet another application of gene therapy that holds great promise in prostate cancer is the stimulation of bone formation by gene therapy (Ad50C-E1a) [57].

9. Antisense therapy

Bcl-2 is a critical regulator of apoptosis in many tissues and is part of a growing family of apoptosis regulatory gene products. Antisense oligodeoxynucleotides such as Genasense therapeutically target genes that play a role in the progression to androgen independence [58,59]. Genasense has been combined with docetaxel in two phase I/II studies with interesting preliminary results [60,61]. It has also been combined with mitoxantrone [62]. A randomised trial of docetaxel and Genasense compared with docetaxel alone by the EORTC is beginning (protocol 30021; C.N. Sternberg study coordinator).

10. Growth factor inhibition

Growth factors are required for cell proliferation. Transfection of growth factors or their receptors can convert normal cells to the malignant phenotype. Many human tumours overexpress growth factors and their receptors, and the hypothesis is that unregulated stimulation of growth factor receptors produces malignancy. Epidermal Growth Factor Receptor (EGFR) regulates angiogenesis, tumour growth, and progression in HRPC.

Inhibition of growth factor receptor kinase-dependent signalling pathways is one of the most promising therapeutic approaches for the treatment of cancer. Aberrant signal transduction plays an important role in the pathophysiology of cancer. Kinases are key enzymes involved in signalling pathways (targets for chemotherapeutic intervention). Growth factor-induced signalling is implicated in the activation of anti-apoptotic cell survival pathways [63].

The EGFR is one of four known related members of a family of growth factor receptors that are mediators of cell growth, differentiation and survival. This family is composed of HER1 (EGFR or ERB1), HER2 (neu or ErbB2), HER3 (ErbB3) and HER4 (ErbB4), some of which have intrinsic tyrosine activity. Enhanced activity of EGFR has been associated with tumour progression in a number of different tumours [64,65]. Levels may vary, dependent upon the detection methods.

A variety of strategies have been developed to therapeutically interrupt signalling at the cellular level and promote cell death. Binding to the EGFR blocks critical signalling pathways and interferes with the growth of tumours expressing EGFR. Therapeutic approaches used to target the EGFR and its signal transduction cascade in prostate cancer include monoclonal antibodies directed against the extracellular binding domain of the EGFR [66], small-molecule tyrosine kinase inhibitors, ligand conjugates, immunoconjugates and antisense oligonucleotides. Agents in clinical development include IMC-C225 (Cetuximab, Erbitux), EMD 55900, ICR 62, ABX-EGF and others that directly block the EGFR [67,68]. In an *in vitro* study, blockade of EGFR by the anti-EGFR antibody ImClone C225 (IMC-C225) inhibited tumour growth and metastasis by inhibiting angiogenesis, and paclitaxel enhanced the results of therapy in HRPC [66].

Low-molecular-weight inhibitors of the EGFR tyrosine kinase include Gefitinib (Iressa; ZD 1839), OSI-774 (Tarceva), PD182905, PKI-166, and CI-1033. Iressa has shown encouraging results in patients with prostate cancer in a phase 1 trial [67], and phase II trials have been initiated. EGFR antagonists have also shown synergy with chemotherapy and with radiation.

In 21 patients in a phase I/II study in HRPC, Iressa was combined with mitoxantrone and prednisone. 5 patients (2/8 on the 250 mg dose; 3/13 on 500 mg) had a PSA response, defined as a PSA decline of $\geqslant 50\%$ lasting $\geqslant 4$ weeks [69].

In another phase I/II trial in HRPC, two doses of Iressa (250 mg and 500 mg) were again combined with docetaxel and Estracyt [70]. In this trial, 30 chemonaise patients were enroled. PSA response was seen in 10/30 (33%), in the 250 group and 5/15 (33%) in the 500-mg group. It appears from these studies that addition of Iressa did not increase the overall toxicity of chemotherapy. Further clinical studies will be required to determine the benefit of this combination over docetaxel and Estracyt alone.

The incidence of HER-2 protein overexpression and its prognostic value are not well characterised in patients with prostate cancer [71]. In a recent study, serum Her-2 neu levels were found to be elevated in 35% of patients with metastatc prostate cancer compared with controls, and PSA levels were higher in the patients with elevated levels [72].

Trastuzumab (Herceptin), a monoclonal antibody binding to the HER-2 receptor was evaluated at the Memorial Sloan-Kettering Cancer Center (MSKCC) and not found to be an effective single agent for prostate cancer. Accurate profiling required metastatic tissue sampling [73]. In another phase I study, trastuzumab was combined with docetaxel and estramustine. HER-2 positivity was not required and 2/6 (33%) patients with measurable disease had objective responses [74].

A novel use of anti-EGFR antibodies includes their combination with other monoclonal antibodies targeting different tumour antigens, such as HER-2. These receptors then heterodimerise upon binding EGFR ligands, resulting in a high-affinity receptor [75]. GW572016 (GlaxoSmithKline) is an oral, potent and selective dual inhibitor of both EGFR and HER-2 that has recently entered clinical trials.

11. Anti-angiogenic therapy

Tumour angiogenesis is a prognostic indicator of the metastatic potential of many cancers. Tumour cell metastases involve changes in tumour cell-to-cell interactions, expression of integrins and expression of metalloproteases (MMPs) [76]. Invasion, proliferation and maturation have become topics for attack in the therapy of prostatic cancer.

It is well recognised that tumour cells require neo-angiogenesis for their growth and metastatic spread [77]. 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).

In prostate cancer, increased vascularisation has been associated with an aggressive phenotype [78] that does not express high levels of FGF and VEGF during tumour progression [79]. However, peptide growth factor-mediated, mitogenic pathways are important in HRPC and their levels can predict outcome [80].

Tumour angiogenesis is a complex process which requires coordinated interactions between numerous proteins, signalling pathways and cell types. Each step provides an opportunity for therapeutic intervention. Strategies to inhibit tumour angiogenesis include: (1) targeting molecules involved in blood vessel formation such as tumour-host derived angiogenic factors or upstream mediators of angiogenic factor expression, such as the ras protein, (2) targeting endothelial cell survival (VEGF, Integrins, Angiopoietin-1), or targeting MMPs. 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.

Prostate cancer is an interesting target for anti-angiogenic therapy. Many agents are currently in clinical development. Trials in prostate cancer have included therapy with Suramin, Carboxyamido-triazole (CAI), thalidomide, CC5013, Endostatin. SU5416, SU6668, Bevacizumab (Anti-VEGFrhuMAb), 2-Methoxyestradiol (Panzem), and TNP-470 [81]. Other agents under development include Endostatin/Angiostatin, VEGF/EGFR inhibitors, cell adhesion inhibitors, and vascular collapse inducers.

The CALGB randomised 393 patients with HRPC to suramin, low intermediate, and high doses (total doses 3.192, 5.320 and 7.661 g/m^2, respectively). Median survival times were 16, 14 and 13 months, respectively ($P = 0.49$). The objective RR were 9, 7 and 15% ($P = 0.10$), and PSA responses were 24, 28 and 34%, respectively ($P = 0.082$). Landmark analyses of PSA decline at 20 weeks showed a statistically significant correlation with survival. High-dose suramin had higher objective and PSA RR, but this was not statistically significant. Toxicity was increased with the higher dose. Patients treated with low-dose suramin had a modest toxicity, making it the preferred arm on this study. The lack of a dose–response relationship and the toxicity profile observed raise serious questions regarding the utility of suramin [82].

Thalidomide is a potent teratogen. *In vitro* data has suggested that it too inhibits angiogenesis, as prostate cancer is dependent on the recruitment of new blood vessels to grow and metastasise. The National Cancer Institute (NCI) has performed a phase II trial of thalidomide in patients with HRPC [83]. Thalidomide was administered either at a dose of 200 mg/day (low-dose arm) ($n = 50$) or at an initial dose of 200 mg/day that escalated to 1200 mg/day (high-dose arm) ($n = 13$). PSA decline $\geqslant 50\%$ was seen in 18% on the low-dose arm and in none of the patients on the high-dose arm. 4 patients were maintained for >150 days. A total of 27% had a decline in PSA of $\geqslant 40\%$, often associated with clinical improvement. Toxicities included constipation, fatigue, neurocortical and neurosensory toxicity. Thalidomide appears to have activity in patients who have failed multiple therapies.

Another study at the NCI evaluated weekly docetaxel 30 mg/m^2 (3 out of 4 weeks) with or without thalidomide 200 mg/day [84]. In a recent update of this trial, 9/24 (38%) receiving monotherapy versus 25/49 (51%) receiving the combination had a PSA response [85]. Combining a cytotoxic agent with an angiogenesis inhibitor is a promising area of investigation for prostate cancer management. In any case, anti-angiogenic therapy is primarily expected to be cytostatic rather than cytotoxic and prolonged intake is thought to be essential.

Trials have also evaluated MMP inhibitors (Marimastat; British Biotech and Prinomastat; AG3340; Agouron). A phase III study compared Prinomastat at two different dose levels (5 and 10 mg orally twice daily) with placebo in patients who had been treated with mitoxantrone and prednisone. Time to PSA progression was 6.8 months in the placebo group ($n = 138$) versus 8.9 months in patients treated with 5 mg ($n = 135$) versus 6.5 months in patients ($n = 134$) treated with 10 mg twice a day. There were no important differences in the PSA response [86].

Panzem's (2-methoxyestradiol) mechanism of action includes upregulation of the death receptor 5 (DR5) in endothelial and tumour cell lines. This induces apoptosis through activation of caspases 3, 8 and 9 and displaces sex hormone binding globulin and inhibits those activities mediated through this protein. Several molecular targets have been proposed to explain the mechanism of Panzem, including its effects on tubulin and on superoxide dismutase [87]. A randomised phase

II trial in HRPC is ongoing at Indiana University and the University of Wisconsin in patients with HRPC. Panzem is also being evaluated alone or combination with a taxane or mitoxantrone.

Endostatin, an endothelin-A antagonist, was originally purified from a haemangioendothelioma cell line. It inhibits endothelial cell proliferation *in vitro*. In a phase I trial, some patients demonstrated decreases in circulating VEGF or changes in contrast enhancement on computed tomography (CT) scan. In a randomised study of 288 patients with HRPC, 10 mg of Altrasentan (ABT-627), a selective endothelin-A receptor antagonist demonstrated a significant delay in time to PSA and clinical progression compared with placebo-treated patients, although no survival benefit was demonstrated in an intent-to-treat analysis [88,89].

SU5416 is a tyrosine kinase inhibitor of Flk-1, a VEGF receptor on endothelial cells. It is a specific inhibitor of VEGFR2 (KDR/Flk1). VEGFR2 is the most important for a proliferative response in endothelial cells. It interferes with the catalytic (ATP-binding) domain of Flk-1 as a putative adenine mimic. Preclinical studies have demonstrated antitumour activity in a variety of cancer xenografts [90]. SU5416 has been evaluated by several authors [81]. Stadler has initiated a study in patients with HRPC. SU5416 was given twice weekly with steroid premedication [91]. The planned accrual is 60 patients.

TNP-470, a fumagillan analogue is a product of fungal contamination that inhibit endothelial cell growth in culture, especially bFGF-driven growth. Its putative target is the type 2 methionine aminopeptidase, and specifically p53/p21-dependent cell-cycle inhibition in endothelial cells. In a phase I dose-escalation trial alternate-day i.v. TNP-470 was given to 33 patients with metastatic HRPC. Although definite activity with TNP-470 was not observed, transient stimulation of serum PSA occurred in some patients [92].

CC 4047, a new analogue of thalidomide, and its novel T cell costimulatory analogues (immunomodulatory drugs) are currently being assessed for the treatment of cancer. However, neither tumour-specific T cell costimulation nor effective antitumour activity has been demonstrated *in vivo* [93].

Another growth factor receptor to be targeted in this disease is the insulin-like growth factor receptor [94] and the platelet derived growth factor. No clinical data are yet available. Definitive insight into the role of these agents in the management of prostate cancer is still under study.

12. Other monoclonal antibodies

Immunotoxin conjugates may use an antibody directed against EGFR or PSMA joined to a cell toxin.

90Yttrium-dota-HUJ591 (90Y-J591) is a radioistope labelled humanised monoclonal antibody (MAB) to the extracellular domain of PSMA [95]. In 20 patients who had failed hormonal therapy or chemotherapy (11 patients). No patients developed HAHA and toxicity was dose-related. PSA responses and objective responses were observed.

In a mouse model, addition of paclitaxel or docetaxel chemotherapy to 90Y-DOTA-peptide-ChL6, in doses clinically achievable in humans, provided therapeutic synergy without increasing toxicity [96]. A phase I trial of 90Yttrium MAB m170, paclitaxel, and cyclosporine followed by autologous peripheral blood stem cell transplantation is in progress.

13. Vitamin D

Clinical activity of Vitamin D (calcitrol (1,25-dihydroxycholecalciferol)) has been reported in HRPC with PSA RR of around 28% [97,98]. The *in vitro* cytotoxic activity of Vitamin D seems to be dose-dependent; however, its clinical hypercalcaemic effect limits clinical dose-escalation of calcitrol. Several agents such as biphosphonates, cortisone, and some chemotherapeutic agents such as carboplatin and paclitaxel can block the hypercalcaemia induced by Vitamin D. The combination of newer more potent biphosphonates, such as Zolandronate, perhaps in combination with Vitamin D, is the subject of ongoing trials [99].

14. Exisulind

Exisulind (Aptosyn), a sulphone metabolite of the non-steroidal anti-inflammatory drug sulindac, is the first of a new class of targeted agents that induce apoptosis (programmed cell death) in a broad range of precancerous and cancerous tissues without affecting normal cells [100]. In a randomised, placebo-controlled study of prostate cancer patients, Exisulind lengthened the median PSA doubling time in men who had increasing PSA levels after radical prostatectomy [101,102].

Because preclinical studies have suggested synergistic interactions between docetaxel (Taxotere) and Exisulind, a phase I/II clinical trial combining these agents has been performed in patients with HRPC [103].

15. Biphosphonates

Bisphosphonates are a class of drugs with a potent bone resorption inhibiting activity that have found increasing utility in treating and managing painful osseus metastases. Zoledronic acid (Zometa) has been

shown effective in the treatment of metastatic blastic disease from prostate cancer as it decreases osteoclast activity in malignant bone. Clinical trials have demonstrated that bisphosphonates have clinical value in the treatment and management of skeletal metastases derived from advanced prostate cancer. Randomised studies in patients with prostate cancer and bone compared with placebo-controlled have now shown that this therapy treats both osteoblastic and osteolytic bone metastases, and clearly decreases the frequency of skeletal complications resulting from bone metastases [104–107].

The molecular mechanisms by which tumour cells metastasise to bone are likely to involve invasion, cell adhesion to bone, and the release of soluble mediators from tumour cells that stimulate osteoclast-mediated bone resorption. Bisphosphonates are powerful inhibitors of osteoclast activity and are, therefore, useful in the treatment of patients with osteolytic metastases. However, an added beneficial effect appears to be their direct antitumour activity!

Several studies with Zometa are ongoing such as the MSKCCC phase I study in combination with calcitrol and a phase II randomised study at the Mayo Clinic of Zoledronate with or without BMS-275291 in HRPC.

16. Conclusions

Biphosphonates and new chemotherapeutic approaches, especially taxane-based combinations, are increasingly of interest in the management of advanced prostate cancer. Prognostic factors reflecting different patient categories must be taken into consideration in the interpretation of clinical trials.

Recent knowledge that prostate cancer is immunogenic has led to new developments in immunotherapy and gene delivery techniques. The reinsertion of inactivated tumour-suppressor genes, inactivation of oncogenes, insertion of immuno-modulatory genes, and insertion of suicide genes will be used to treat prostate cancer.

Molecular targeted small molecule therapy and monoclonal antibodies are dominating contemporary clinical trials. The steps in signalling cascades have provided multiple opportunities to interrupt signalling and have identified a variety of targets for therapeutic intervention. In addition, anti-angiogenic agents and several new chemotherapeutic agents that work at different points in the cell cycle seem promising. With the caveat that the results must be corroborated in phase III trials, prospects for the future are hopeful.

The medical management of prostate cancer is being revolutionised by experimentation with new molecules. Understanding of the molecular biology of prostate cancer is helping to direct therapeutic choices. Strategies will continue to develop for the use of the new biological agents.

The major challenge for the near future is to find the means to improve the delivery of genes, both locally and systemically. Furthermore, combinations with other modalities should be developed.

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