Systemic treatment and new developments in advanced prostate cancer

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Introduction

Prostate cancer is the most common cancer in American men, and the second leading cause of death, after lung cancer. The American Cancer Society has estimated that there would be about 198,100 new cases of prostate cancer in the United States in 2001, and about 31,500 deaths [1]. In Europe, prostate cancer represents the second most frequent cause of death in men, along with colorectal cancer [2]. Data from the European Network of Cancer Registries on the incidence and mortality rates in 23 European countries show a significant increase in incidence and mortality rates in elderly patients, and a significant upward trend in incidence in the younger and middle aged groups. This differs from the USA, where decreasing mortality rates have recently emerged, partly attributable to the changes of patterns of care, suggesting a potential effect of preventive screening measures [3].

In fact, the diagnosis of prostate cancer has increased dramatically over the past few years owing to the ageing population, heightened public awareness, screening programs, widespread use of prostate-specific antigen (PSA), and advances in imaging techniques. Early diagnosis may be aided in the future by genetic markers such as the *HPC1* gene or the candidate prostate cancer susceptibility gene at chromosome 17p which has recently been identified [4–6].

Eighty-nine percent of men with prostate cancer live at least five years, and 63% survive at least ten years. Once cancer has spread, 5-year survival is around 31%. Prostate cancer encompasses a wide range of diseases where the biological properties of the tumour predicts prognosis. Controversy surrounds the optimal management of patients with all stages of prostate cancer. For metastatic disease, hormonal therapy is usually the treatment of choice, although there is controversy surrounding what is the optimal therapy and timing. For patients who have become refractory to hormonal therapy, new therapeutic strategies are under evaluation. Interest has focused upon methods of tailoring endocrine therapy in ways that offer the individual patient an optimal combination of quality of life and anticancer efficacy. For patients with locally advanced prostate cancer neo-adjuvant and adjuvant hormonal therapy have been the subject of several studies [7,8], and chemotherapy in high-risk patients has become an exciting new avenue of investigation. This article will review the medical therapy of prostate cancer with an emphasis upon chemotherapy in hormone-refractory prostate cancer (HRPC) and in locally advanced disease.

Advanced disease

Approximately 30–35% of patients with prostate cancer will present with regional or metastatic tumours, while an additional 25% will develop metastases in the course of the disease. Metastases are commonly to bone, where the lesions can be seen on X-ray as osteosclerotic lesions or on a bone scan as areas of increased activity known as 'hot spots'. In patients presenting with metastatic disease and receiving androgen ablation, median survival is 2.5 years, but this is entirely dependent upon prognostic factors [9].

Hormone-naive disease

Palliative androgen ablation produces objective tumour regression in soft tissue sites in approximately 80% of patients, normalization of an abnormal PSA in 70%, and an improvement in the bone scan in 30% to 50% of cases [10].

Orchiectomy has been the gold standard endocrine therapy for many years. However, in most parts of Europe, for psychological and cultural reasons, medical therapy is considered to be more acceptable to patients than surgical castration. Currently, gonadotropin-releasing hormone (GnRH) agonists such

as goserelin, leuprolide and triptorelin are the most frequently used androgen ablation therapy. These are often combined with an anti-androgen to prevent flare related to a temporary surge of luteinizing hormone (LH) and testosterone.

Non-steroidal anti-androgens such as, flutamide, bicalutamide, and nilutamide directly block the androgen receptor, and act directly on prostatic cells. Treatment with anti-androgens alone may avoid the loss of sexual potency. Combined androgen blockade (CAB) is a means of blocking the adrenal androgens. The main advantage to the combination of an LHRH analogue and an anti-androgen is blockade of the LHRH agonist flare.

Whether or not CAB is really necessary has been the subject of intense investigation. Only three studies have demonstrated a positive effect due to CAB. In the National Cancer Institute (NCI) Intergroup trial, androgen blockade with leuprolide and flutamide resulted in longer progression-free survival and overall survival than leuprolide alone in patients with minimal disease and good performance status [11]. In a subsequent European Organization for Research and Treatment of Cancer (EORTC) trial, goserelin and flutamide were associated with a longer time to objective progression and longer survival than orchiectomy alone [12]. In a third trial, nilutamide plus orchiectomy was more effective than orchiectomy alone for metastatic prostate cancer [13]. However, for patients with widespread bone or soft tissue metastases and a poor performance status, responses have been characteristically short, and CAB appeared to not provide a significant advantage over LHRH agonists or orchiectomy alone.

When a meta-analysis of 8275 patients (88% metastatic and 12% locally advanced) in 27 randomized trials was performed, 5-year survivals of 25.4% with CAB and 23.6% with androgen suppression (monotherapy) alone, were obtained. This represented a non-significant gain of 1.8% (logrank $2P = 0.11$). CAB, with addition of an anti-androgen to androgen suppression, improved 5-year survival by about 2% or 3%, but the range of uncertainty as to the true size of this benefit was from 0% to 5% [14].

These data and those of other meta-analyses suggest a higher toxicity rate and decreased quality of life with CAB. An additional disadvantage is that available LHRH analogues and pure anti-androgens are expensive. For these reasons, the routine use of anti-androgens in combination with medical or surgical castration as first-line hormonal therapy in patients with metastatic prostate cancer is not justified [15].

Intermittent hormonal therapy

Nearly all prostate cancers treated with hormonal therapy eventually become resistant to this treatment over a period of months or years. Constant exposure to hormonal therapy may promote resistance, and therefore intermittent treatment has gained popularity. With intermittent therapy, hormonal therapy is discontinued after PSA levels return to normal. If the PSA level begins to rise, the therapy is started again. Clinical trials of intermittent hormonal therapy are still in progress and it is too early to say whether this new approach is better or worse than continuous hormonal therapy. However, one advantage of intermittent treatment is that the side-effects of hormonal therapy (such as impotence, hot flashes and loss of sex drive) are avoided for a while [16].

LHRH Antagonists

The GnRH antagonists are a new therapeutic class of agents that directly block pituitary GnRH receptors that immediately reduce testosterone to castration levels and are given as monotherapy. Two phase II trials and 3 phase III trials have been conducted with aberelix both in Europe and in the US [17–20]. These antagonists produce a fast decrease in prostate volume, rapid decrease in PSA, without a surge in testosterone and rapid testosterone recovery upon suspension. Questions arise as to the expense and tolerability of the depot formulation.

Hormone-refractory prostate cancer

Hormone-refractory prostate cancer (HRPC) is defined as 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, with median survival in older studies of approximately 6 months afterwards [21]. What are the options for men who progress under endocrine treatment?

Options for patients with HRPC include: second-line hormonal therapy, chemotherapy with or without endocrine therapy, palliative therapy (radiation therapy, Strontium 89 analgesic therapy, and biphosphonates) and investigational therapies.

Bone is the primary and only site of metastases in 65% of patients who present with metastatic prostatic cancer. For this reason, objectively measurable criteria for response evaluation are often lacking. In many patients, bone pain and decreased performance status are predominant, and relief of these symptoms is as important as prolongation of survival.

Contemporary trials suggest that prostate cancers are not as resistant to therapy as previously believed.

This is due in part to the change in reporting of results in prostate cancer. Many older trials didn't use PSA and results were not very interesting because they often included patients with stable disease as responders.

Use of surrogate endpoints such as reduction in PSA or improvement in pain have been used to evaluate new agents. Quality of life evaluations have also become a fundamental part of many prostate cancer studies.

A durable reduction in PSA of 50% or greater has only recently been accepted as providing a reasonable indication of the activity of a treatment [22]. Although the value of PSA decline as a measure of therapeutic benefit has not been definitively established, a sustained reduction in PSA has been shown to correlate in several studies with survival [23–25].

Problems with the interpretation of post-therapy PSA arise because a drug may decrease PSA release 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 accounted for in the clinic 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 proceed a decline [26].

Second-line hormonal therapy

Second-line hormonal treatment works by diminishing circulating adrenal androgens. This may cause tumour regression by suppressing any remaining hormone-dependent prostatic cancer cells. Relief of symptoms may occur rapidly, suggesting a mechanism 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 [9]. 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' [27]. Up to 40% of patients failing CAB will respond when the anti-androgen is discontinued. This paradoxical response was first documented with flutamide withdrawal, but was subsequently shown to occur with other non-steroidal anti-androgens. Mutated androgen receptors (AR) can be found in 50% of metastatic prostate cancers. Long-term androgen ablation with anti-androgens may lead to increased expression and activity of the AR [28]. This may explain why discontinuation of the anti-androgen may lead to a decrease in PSA.

Nonetheless, high doses of bicalutamide (150 mg daily) may be effective in some patients [29]. Megace or dexamethasone are other second-line hormonal therapies, which may produce symptomatic improvement and disease regression. Objective responses vary from 10–30% [9].

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, edema, hepatotoxicity and rash in 4–10% of patients [30]. As part of a larger Cancer and Leukaemia Group B (CALGB) study, 250 patients were treated with anti-androgen withdrawal followed by ketoconazole and hydrocortisone at progression.

In combination with doxorubicin (Adriamycin®), a >50% decrease in PSA was seen in 57% of patients in a study from the MD Anderson Hospital. In this particular study, cardiac and mucocutaneous toxicities were reported [31].

Complementary and alternative methods

Alternative methods have become increasing popular, although often not always supported by clinical trials. PC-SPES, a combination of 8 Chinese herbs may act through a hormonal mechanism [32,33]. An extract of PC-SPES induces apoptosis of hormone-sensitive and-insensitive prostate cancer cells in vitro, and suppresses the growth of a hormone-insensitive prostate cancer cell line in vivo.

PC-SPES was evaluated in 33 patients with HRPC and 37 patients with androgen-dependent prostate cancer. All patients with hormone-dependent prostate cancer had a PSA decline of >80%, with a median duration of 57+ weeks, and 97% had testosterone declines to the anorchid range. Nineteen (54%) of 35 HRPC patients had a PSA decline of >50%, including 8 (50%) of 16 patients who had received prior ketoconazole therapy. Toxicities included thromboembolic events, allergic reactions and gynecomastia [34]. Further study is required to determine whether its effects exceed those expected with oestrogen therapy, but PC-SPES seems to have activity in both hormone-dependent and HRPC.

Chemohormonal therapy

Estramustine (Estracyt®), is the combination of a chemotherapeutic agent, Nornitrogen mustard, and a

hormone, Estradiol. Overall response rates have varied from 0–40% [35].

Estramustine is synergistic with the vinca alkaloids, epidophyllotoxins, and taxanes and inhibits microtubules by a different mechanism than the vinca alkaloids. It is not cross-resistant with these agents, and bypasses the multi-drug-resistance phenotype. It also has non-overlapping toxicity, which is primarily gastrointestinal, with other cytotoxic agents. Advantages include the oral administration and lack of myelosuppression. Disadvantages are related to thromboembolic events.

When estramustine was combined with vinblastine in 3 separate phase II trials, cumulative data revealed a >50% decrease in PSA in 46–61% of patients, with measurable disease regression in 24% [36,37]. Two phase III randomized studies of the combination were published. An American study revealed a benefit to the combination compared to vinblastine alone [38], while an EORTC study comparing the combination to estramustine alone was discontinued due to toxicity, and found no overall difference [39].

Chemotherapy

There has been a wide disparity in results obtained with chemotherapy in HRPC [9]. Objective tumour regression in older studies was reported in <10% to 20% [40]. Median survival from study to study has been similar, 30 to 40 weeks. No agent or regimen has shown a consistent impact on survival, and because of this no standard chemotherapy regimen has been defined. Newer agents and combinations, used in era of PSA, however, seem to show promise.

For many years, low dose weekly doxorubicin 20 mg/m^2 was considered as first-line chemotherapy for HRPC in the US. In Europe, a doxorubicin analogue, epirubicin, was often substituted. Response rates for doxorubicin have ranged from 0 to more than 50%, depending upon the response criteria utilized. Mitoxantrone, another anthracycline, also has become increasingly recommended following two randomized trials of mitoxantrone plus prednisone or hydrocortisone [41,42]. Both trials observed palliation yet no survival benefit. This may be explained by the fact that both trials employed crossover designs. The primary endpoint of a Canadian trial was a palliative response described as a decrease in analgesic use. Based on the result of this trial, the combination was approved by the food and drug administration (FDA) for the palliation of pain [41]. For this reason, many clinicians consider this regimen to be the standard against which other approaches should be compared.

Most recently, the taxanes have gained increasing usage in the treatment of HRPC. Both paclitaxel (Taxol®) and docetaxel (Taxotere®) work by promoting microtubular assembly and inhibiting disassembly [43–45]. Trials containing a taxane can be found in Table 1.

Based on the assumption that agents that inhibit microtubules may work well together, the combination of estramustine and either paclitaxel or docetaxel has garnered interest and been evaluated in varying schedules. The combination of estramustine plus a 96-hour infusion of paclitaxel, revealed a 50% or more 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 [46].

Table 1
Phase II trials of taxanes in hormone-refractory prostate cancer

Author	Year	Therapy	*N*	>50% PSA response	Objective RR
Hudes [46]	1997	E + P	34	53%	44%
Savarese [54]	1999	E + D	40	69%	23%
Petrylak [51]	1999	E + D	33	63%	28%
Kelly [57]	2001	E + P + C	56	67%	45%
Smith [85]	1999	E + VP-16 + P	37	65%	45%
Kreis[a] [52]	1999	E + D	17	82%	17%
Sinibaldi [53]	2000	E + D	29	45%	23%
Picus [44]	1999	D	35	46%	28%
Friedland [86]	1999	D	21	38%	–
Roth [43]	1993	P	23	0%	4%
Trivedi [45]	2000	P[b]	18	39%	50%

E = Estramustine (Estracyt®), P = Paclitaxel (Taxol®), D = Docetaxel (Taxotere®), C = Carboplatin, RR = response rate, PSA = prostate-specific antigen, VP-16 = etoposide.
[a] Phase I/II study.
[b] Administered weekly.

Estramustine and paclitaxel have also been combined with etoposide (VP-16), a podophyllotoxin derivative, known to inhibit topoisomerase II at the nuclear matrix level [47]. Although estramustine is best known as an antimicrotubule agent, it also acts synergistically with etoposide [47–50]. The mechanism of action may be different from that in combination with vinblastine, and the results are of interest in view of the limited activity of any one of the agents alone.

Encouraging data have also been reported with docetaxel given every 3 weeks and estramustine. Evidence of the activity of docetaxel and estramustine combinations include a PSA response in the range of 45–82%, and objective measurable response in the range of 17–28%, improvement in the Karnofsky performance status score or pain symptoms control in the range of 53–88% [51–54]. Survival data are usually not reported with the exception of one phase I trial in which median survival of 22.8 months was observed in patients mostly previously treated with prior chemotherapy [51]. The safety profile of the combination appears acceptable.

Most recently, efforts have been focused upon the optimal schedule of paclitaxel and docetaxel with lower does of estramustine. For this reason, there is interest in the weekly administration of either paclitaxel or docetaxel [45,55,56]. Preliminary data have been extremely promising and require further exploration.

In this context, an international industry sponsored trial will recruit 804 men with HRPC, who will be randomized to receive 'standard therapy' consisting of mitoxantrone + prednisone versus docetaxel + prednisone. Docetaxel will be administered in two different ways — either every three weeks or weekly. The primary end-point is survival, while the secondary end-points are the response rate and quality of life.

Meanwhile, an ongoing Southwest Oncology Group (SWOG) phase III randomized trial is focusing upon the combination of estramustine and docetaxel as compared to mitoxantrone and prednisone in HRPC, and will enroll 620 patients.

While several groups have reported significant efficacy and minimal toxicity in patients with HRPC receiving estramustine plus docetaxel or paclitaxel, others have demonstrated single-agent activity of platinum compounds in HRPC. Recent interest has also been focused upon the combination of these agents with carboplatin. The combination of estramustine, a taxane, and carboplatin is currently under investigation in three separate trials of HRPC. The first is a Dana-Farber Cancer Centre trial of escalating doses of weekly docetaxel, and the second study is a CALGB multicentre phase II study evaluating the combination of estramustine, docetaxel, carboplatin, and granulocyte-colony stimulating factor (G-CSF).

The third was a multi-institutional endeavour led by Memorial Sloan-Kettering Cancer Centre in which 56 patients with progressive HRPC were treated with the combination of estramustine, paclitaxel and carboplatin [57]. A >50% decrease in PSA was seen in 67% of patients. Of the 33 patients with measurable disease, 2 (6%) had a complete response and 13 (39%) had a partial response. The overall median time to progression was 21 weeks, and the median survival time for all patients was 19.9 months. Major grade 3 or 4 adverse effects were thromboembolic disease in 25%, hyperglycaemia in 38%, and hypophosphataemia in 42%. The regimen was deemed to be active and the toxicity well tolerated.

Future research will focus upon the combination of agents such as the taxanes with newer more targeted therapies such as Herceptin [58].

Suramin

Palliation of pain with decline in PSA was shown with the growth factor inhibitor suramin in combination with hydrocortisone. Until now, there has been wide variability in response rates, and in reports of neurotoxicity. In a large cooperative group trial of suramin plus hydrocortisone versus hydrocortisone and placebo, pain relief and anti-tumour effect may be dissociated. No survival benefit was seen in this trial conducted with a crossover design [59,59]. The mechanisms of suramin-mediated antitumour activity still need to be clarified.

Small cell carcinoma of the prostate

A neuroendocrine component of cells in the prostate has been recognized. Cells with neuroendocrine features may produce a variety of neuropeptides such as serotonin, bombesin and others that regulate tumour growth and metastatic potential. Small cell carcinoma of the prostate is a subtype of prostate cancer, which often presents with advanced disease and does not respond to hormones. It is also the most frequent acquired phenomenon in patients who initially present with adenocarcinoma of the prostate. This entity should be considered in patients who have rapidly progressing disease, visceral metastases and a disproportionately low PSA. Patients should be treated with chemotherapy, using regimens for small cell carcinoma of other sites, such as etoposide and cisplatin [60].

Localized prostate cancer

In the US, 58% of all prostate cancers are discovered while they are still confined to the prostate [61]. Management options include radiation therapy (RT), radical surgery and conservative management. The ideal approach for all patients remains unclear, as a definitive prospective randomized trial has never been performed.

The majority of men receiving radical treatment will survive 10 years following optimal RT or radical prostatectomy. RT is often selected for patients with coexisting medical problems that would preclude major surgery. The strategy of initial conservative management and delayed hormone therapy is an alternative for elderly patients with grade 1 or 2 minimal volume tumours [62,63].

Adjuvant and neo-adjuvant hormonal therapy

Most studies on adjuvant hormonal therapy after radical prostatectomy in locally advanced prostate cancer, have been small and non-randomized, but have suggested an improvement in disease-free survival [64].

In a frequently quoted American study, 98 node-positive patients after radical prostatectomy were randomized to intermediate versus delayed hormonal therapy. At a median follow-up of 7.1 years, 14.8% of men who received immediate anti-androgen treatment had died, compared with 35% of men treated at the time of progression ($P = 0.02$) [65]. In this study, immediate anti-androgen therapy after radical prostatectomy and pelvic lymphadenectomy improved survival and reduced the risk of recurrence in patients with node-positive prostate cancer.

A similar trial from the MD Anderson Cancer Centre and the Eastern Cooperative Group (ECOG) is investigating adjuvant hormonal therapy compared with observation in surgically treated node-negative high-risk patients. The end-points are an increase in relapse-free survival, disease-specific and overall survival, and quality of life. This study is designed to detect a 15% decrease in the recurrence rate at 5 years from 50% to 35% in 496 patients (90% power).

The Early Prostate Cancer program is composed of 3 separate trials, designed and powered to enable combined analysis. This constitutes the largest clinical trial in localized prostate cancer (T1b-4N0-1M0). Single agent bicalutamide (Casodex®) 150 mg daily has been prospectively compared to placebo in 8113 men entered over 3 years, the majority of whom had node-negative (N0) disease [66]. Preliminary results of the first trial (0024) reveal objective clinical progression in 181/1798 (10.1%) of the bicalutamide group compared to 293/1805 (16.2%) of the watchful waiting group, representing a 43% reduction ($P < 0.0001$) in the risk of disease progression compared to placebo. Overall survival data are immature, with a low prostate cancer mortality rate [67]. These trials are expected to provide information on the role of bicalutamide monotherapy as an addition to standard care for patients with local prostate cancer who have received a therapy of curative intent.

Neoadjuvant, as opposed to adjuvant hormonal therapy, prior to radical prostatectomy has also been evaluated in several randomized trails. Most studies have consistently found that this approach decreased the rate of positive margins, but did not impact on disease-free or overall survival [68,69].

In terms of RT, hormonal therapy has been shown to improve local control and survival in patients with locally advanced prostate cancer. It must be understood that patients selected for RT tend to be older and have higher-grade, higher stage tumours and higher PSA levels. Younger, healthier men with smaller, localized tumours have historically tended to undergo surgery. For example, in a study of 287 patients with locally advanced prostate cancer who were treated with conventional external beam RT and followed for 15 years, overall survival was only 23% [70]. Investigators have therefore tried to add hormonal therapy to these poor risk patients.

Adjuvant hormonal therapy when started simultaneously with RT improves local control and survival. This has been confirmed in two studies [71,72]. The exact length of exposure remains controversial, and an ongoing trial in the EORTC is evaluating 6 months of hormonal therapy versus 3 years, while another Canadian trial is studying 3 months versus 8 months of therapy [73].

Chemotherapy in localized prostate cancer

The prognosis of localized prostate cancer is related to Gleason grade, PSA level and TNM staging. Poor risk locally advanced prostate cancer is defined by the parameters of PSA >20 ng/ml, Stage > T3–4, and Gleason score 8–10 [74]. Poor risk locally advanced prostate cancer has a mortality rate of 75%. Since long-term local control is essential, an important requirement for improvement of this poor outcome is the achievement of local control of the primary tumour.

New approaches aimed at better local control are required. In addition, since locally advanced prostate cancer is usually associated with systemic disease at the time of diagnosis, there is little doubt that

Table 2
Clinical trials of neoadjuvant and adjuvant chemotherapy in locally advanced prostate cancer

Author	Year	Therapy	N	Results
Pettaway [75]	2000	K + A alternating with E + V + RP + CAB	30	Did not achieve 20% pT0
Clark [76]	2001	E + VP-16 + RP	18	Well tolerated
Zelefsky [77]	2000	E + V + 3D CRT	27	Increased late G2 GI and GU toxicity
Ben-Josef [78]	2001	E + VP-16 + RT	18	Well tolerated
SWOG 9921	Ongoing	CAB + RP vs. CAB + RP + M + P	1360	Phase III
RTOG 99-02	Ongoing	P + E + VP-16 + RT + AS vs. RT + AS	1440	Phase III

K = Ketoconazole, A = doxorubicin (Adriamycin®), E = Estramustine (Estracyt®), V = vinblastine, VP-16 = etoposide, P = Paclitaxel (Taxol®), C = carboplatin, M = mitoxantrone, P = prednisone, RP = radical prostatectomy, 3D CRT = 3 dimensional conformat radiotherapy, AS = androgen suppression, CAB = combined androgen blockade, SWOG = South Western Oncology Group, RTOG = Radiation Therapy Oncology Group, G2 = grade 2, GI = gastrointestinal, GU = genitourinary.

systemic therapy will be necessary to improve the outcome of this disease. For poor risk patients, combined neoadjuvant chemotherapy and hormonal therapy prior to radical prostatectomy or radical radiotherapy is a new strategy that has newly gained momentum. Some of the Phase II and III trials in locally advanced prostate cancer are found in Table 2.

Neoadjuvant chemohormonal therapy and radical prostatectomy with CAB combined with ketoconazole and doxorubicin alternating with estramustine and vinblastine was evaluated at the MD Anderson Cancer Centre [75]. This approach was feasible, although the goal of achieving a 20% pT0 status was not achieved.

In another Phase II trial of neoadjuvant estramustine and etoposide, acceptable surgical morbidity was confirmed in 18 patients who underwent radical prostatectomy after chemotherapy [76]. The regimen was associated with estramustine-induced thromboembolic toxicity. Pathologic analysis suggested a higher than expected rate of organ-confined and specimen-confined disease, but little evidence of antitumour effect beyond that associated with androgen deprivation. Additional study of this paradigm, of chemohormonal therapy followed by radical prostatectomy, with other drug regimens is warranted.

In fact, this concept is being evaluated in the SWOG study 9921 comparing adjuvant hormonal therapy with chemohormonal therapy (CAB plus mitoxantrone and prednisone) in surgically treated high-risk disease. Patients with Gleason score >8, pT3b-T4 and/or N1 or Gleason score 7 with extraprostatic extension or positive surgical margins are eligible. The end-points are survival, relapse-free survival and toxicity. This study is designed to detect a 30% increase in median survival at 10 years to 13 years in 1,360 patients (90% power).

Chemohormonal therapy associated with RT in high-risk patients is also a therapeutic option in unfavourable-risk prostate cancer. Neoadjuvant and concomitant estramustine and vinblastine were combined with high-dose three-dimensional conformal radiotherapy (3D-CRT) [77]. Therapy consisted of three 8-week cycles of estramustine and vinblastine and 8 weeks of 3D-CRT, with estramustine given orally and continued until the completion of 3D-CRT to a dose of 75.6 Gy. Although the incidence of modest gastrointestinal (GI) and genitourinary (GU) toxicities was increased, no severe toxicities were encountered with this regimen.

In a similar study, concurrent estramustine and definitive RT followed neoadjuvant estramustine and etoposide. Actuarial 3-year overall survival and disease-free survival were 88% and 73%, respectively. Local control rate, assessed by repeated prostate biopsies at 18 months after therapy, was 71% [78].

A phase III Radiation Therapy Oncology Group (RTOG) trial 99-02 is evaluating androgen suppression and radiation therapy with or without paclitaxel, estramustine, and VP–16 in localized high risk prostate cancer patients. Eligibility criteria include PSA 20–100 ng/ml and Gleason Score >7 (any T stage) or clinical stage >T2 and Gleason Score >8 (PSA <100 ng/ml) (M0). The end-points are survival, biochemical control, relapse-free survival, freedom from distant metastases and toxicity. The study is designed to detect a 6% increase in survival from 79% to 85% at 5 years. Accrual of 1,440 patients to this study is expected to take 6 years.

Palliative systemic therapy

Bone pain is often a debilitating component of metastatic prostate cancer and should be approached systematically. Focal irradiation to palliate bone pain for solitary painful bone metastases may be supplemented by hemibody irradiation for the palliation of widespread metastases. After allowing for adequate recovery, the alternate half-body can be irradiated. Side-effects include nausea, vomiting, diar-

rhoea, haematologic abnormalities and pneumonitis. In one study, 82% receiving upper hemi-body and 67% receiving lower half-body irradiation remained pain free until death [79].

Available therapeutic modalities that use either radionuclides or bisphosphonates can effectively and safely be used in the palliative management of metastatic prostate cancer. Strontium^{89} has been found to be effective in palliating bone pain, with subjective response in >75–80% of patients. This bone-seeking radionuclide, has a high uptake in osteoblastic metastases, and remains in the tumour sites for up to 100 days, decaying by beta-particle emission [80]. It may be most useful in combination with RT in delaying the development of new lesions [10,80]. Other radionuclides such as Rhenium^{186} and Samarium^{153}, conjugated to ligands with affinity to the bone emit both gamma energies that provide images and beta energies that are therapeutic [10]. CYT-356, conjugated with yttrium^{90}, a beta-emitter has been used in the US for diagnosis of occult metastatic disease [81].

Strontium^{89} has been used not only as palliative therapy, but also as consolidation therapy in patients with HRPC. 103 patients received induction chemotherapy with ketoconazole and doxorubicin alternating with estramustine and vinblastine. After 2–3 cycles, 72 patients who were clinically stable or responders were randomized to receive doxorubicin with or without strontium^{89} weekly for 6 weeks. Overall, 62 of the 103 (60%) of patients had >50% reduction in PSA; 49 (52%) patients with bone pain had complete resolution of pain. For the 36 patients assigned to receive strontium^{89} and doxorubicin, median survival time was 27.7 months compared to 16.8 months in 36 patients treated with doxorubicin alone ($P = 0.0014$); hazard ratio 2.76 (95% confidence interval (CI) 1.44–5.29). In this study, bone-targeted consolidation therapy given to patients with stable or responding HRPC after induction chemotherapy, improved overall survival [82]. This represents an interesting observation concerning adjuvant strontium that should be verified by further studies.

The rationale for using biphosphonates in metastatic prostate cancer is not immediately obvious, given that most metastases are osteoblastic. However, biphosphonates can relieve pain caused by bone metastases, and may also slow the growth of these metastases. The clinical use of these agents is based upon observations that provide ample evidence that, in prostate cancer, the metastatic process is associated with increased bone resorption. Evidence regarding the beneficial effects of biphosphonates in reducing morbidity from metastatic prostate cancer is reasonably solid, although the choice of optimal bisphosphonate, mode of administration, dose and duration of treatment must be determined in large, controlled studies before their widespread clinical use can be advocated [83,84]. Studies of newer biphosphonates involve shorter administration times and target patients with established metastatic disease, and patients with local disease at high risk of relapse.

Neither radionuclides nor biphosphonates have definitively been shown to prolong survival in patients with prostate cancer, but both agents have the potential to beneficially alter the metastatic process.

Conclusions

HRPC remains a challenge, but this disease may not be as resistant as previously thought. Investigations are currently under way evaluating neoadjuvant and adjuvant chemohormonal therapy in patients with poor prognosis localized prostate cancer. The use of promising chemotherapy agents earlier in high-risk localized disease may improve clinical outcomes in these patients by decreasing their risk for systemic relapse. The heterogeneity in the hormone responsiveness of prostate cancer, the availability of several new active chemotherapy combinations, and the refinement in risk prediction have stimulated a series of questions that hopefully will be addressed by future research efforts.

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