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Clinical Oncology Update: Prostate Cancer

Evolving Strategies of Cytotoxic Chemotherapy for Advanced Prostate Cancer

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Despite the use of cytotoxic chemotherapy for advanced prostate cancer for half a century, its clinical utility in this setting remains undefined. Based on traditional methods of assessment, the list of the most active cytotoxic agents includes cyclophosphamide, doxorubicin, mitoxantrone and cisplatin. With the introduction of more structured methods of assessment, including careful assessment of indices of quality of life and serial measurement of serum prostate-specific antigen (PSA), the role of cytotoxic agents is being re-assessed. In view of the cell cycle characteristics of prostate cancer, there appears to be an emerging role for combination inhibitors of mitosis, including estramustine in combination with the vinca alkaloids, etoposide or paclitaxel. © **1997 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

DESPITE THE progress in the diagnosis and management of early stage disease, the management of advanced prostate cancer remains an important problem. The proportion of cases diagnosed at an early stage has increased to more than 70% [1]. However, this figure represents a shift in demography due to an increased absolute number of cases of stage A-B cancer, without a reduction in the number of incident cases of advanced disease. As there has been relatively little progress in the conceptual basis of management of advanced disease since 1941, when Huggins and Hodges demonstrated the effectiveness of androgen ablation in the treatment of prostate carcinoma [2], the majority of patients presenting with advanced cancer are still destined to die of their disease.

Despite improving the survival of patients with many different malignancies, chemotherapy has traditionally played a relatively minor role in the management of prostate cancer. Most early trials have shown a relative lack of efficacy and considerable toxicity [3, 4], although the interpretation of results, prior to development of prostate-specific antigen (PSA) measurement, was limited by the lack of adequate indices of response [5]. However, with development of new drugs, new methods of evaluation [6] and increased knowledge of the biology of prostate cancer, there has been a renewed interest in the possible role of non-hormonal systemic treatment in management of this disease.

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HETEROGENEITY OF THE DISEASE

In order to evaluate the potential impact of chemotherapy for the management of prostate cancer, one needs to take into account the heterogeneity of this disease. The biology of the tumour varies not only between individuals, but also between different stages of the disease within the same individual. This may have important implications on the variability of therapeutic response in patients with early versus metastatic disease.

It has been shown that at the time of diagnosis, prostate cancer masses are composed of several cellular subpopulations, including an initial clonal expansion of androgen independent cells [7]. As hormone resistance evolves, the relative proportions of these different subpopulations change [8]. There have also been a variety of histologically distinct subsets detected in prostate cancers, including small cell anaplastic carcinoma, carcinoid and transitional cell carcinoma, which are fundamentally resistant to hormonal manipulation. It has been shown that prostatic tumours that are very sensitive to chemotherapy often contain a significant proportion of cells of small cell or neuroendocrine

morphology [9]. Approximately 10% of prostatic carcinomas have been reported to have neuroendocrine differentiation. Although most of these actually represent adenocarcinomas with areas of neuroendocrine differentiation, 1–2% of these are true neuroendocrine small cell carcinomas of the prostate. They are characterised by a rapid pace of the disease, that parallels that of small cell carcinoma of the lung [9]. Syndromes of ectopic hormone production, including hypercalcaemia, occur frequently in these tumours [10, 11]. PSA levels correlate poorly with the extent of disease. Other markers, such as CEA (carcinoembryonic antigen) and LDH (lactate dehydrogenase) have been found to be elevated in 65 and 76% of patients, respectively [10]. Patients with small cell cancers are more likely to have visceral involvement, with less frequent osseous metastases and, although more likely to respond to chemotherapy, they have a shorter survival than those with classical adenocarcinoma of the prostate [10–12].

Another feature that can be variable between tumour cells is cell growth kinetics. Prostate cancer cells often exhibit Gompertzian growth characteristics with progressive slowing of cell growth rate, as the tumour volume increases. This has important implications in terms of assessment of response—tumours that are slowly growing may give the impression of stable disease when, in fact, the tumour is slowly progressing. In addition, these kinetic characteristics are relevant to the choice and schedule of treatment as the majority of cells may not be replicating, and are thus more likely to respond to drugs that are not S phase-dependent and to drugs that are delivered over a prolonged period of time. The prolonged doubling time characteristic of prostate cancer cells may also explain the difference in cytotoxic response between prostate cancer and other hormone-responsive malignancies (such as breast cancer).

It has been demonstrated that androgen-independent growth in prostate cancer may, in part, be secondary to production of peptide growth factors regulated by autocrine and paracrine mechanisms [13]. Expression of the epidermal growth factor receptor (EGFR) has been shown to be upregulated in prostate cancer [13, 14]; prostate cancer cell lines may express their own growth factors (e.g. TGF alpha) which can bind to the EGF receptor and may be partially responsible for androgen-independent tumour growth.

Prostate cancer regression after androgen blockade occurs by apoptosis—active cellular death where cells participate in their own demise, a process that is distinct from passive cellular death where environmental perturbations lead to cellular lysis [15]. However, androgen independent prostate cancer cell lines do not appear to participate in the apoptotic pathway of cell death in response to androgen ablation, and it may be that other factors may play a role in tumour resistance. In this context, point mutations have also been demonstrated within the androgen receptor gene [16], which may alter receptor function.

ASSESSMENT OF OUTCOME

The problem with most of the initial studies of chemotherapy in prostate cancer was that the response criteria used did not reflect changes in tumour volume and did not provide information about the benefit to the patient. Since then, a number of studies have used PSA as a surrogate marker of tumour load, or the formal assessment of pain by a physician as an index of patient benefit [17–20]. The most recent studies have used more specific indices of performance status and symptomatology to provide more objective indicators of symptomatic response [21].

Table 1. Confirmation of 'true' hormone resistance

Time frame	Parameters
Presentation	Assess symptoms & signs Measure PSA, PAcP, SAP, (LDH?) Document prior hormone therapy Establish compliance
Biochemical baseline	Check LH/FSH/testosterone/DHEA
follow-up	Clinical monitoring PSA (other markers?) LH/FSH/DHEA

PSA, prostate-specific antigen; PAcP, prostatic acid phosphatase; SAP, serum alkaline phosphatase; LDH, lactate dehydrogenase; LH, luteinising hormone; FSH, follicle-stimulating hormone; DHEA, dehydroepiandrosterone.

In recurrent and metastatic prostate cancer, standard methods of response assessment are difficult to apply as the majority of metastatic deposits are osseous, and thus difficult to quantify. Only 10% of patients with metastatic cancer of the prostate have measurable visceral disease and these patients may have a different response pattern from the patients who have bony disease [4, 8]. The use of surrogate markers of response, such as serial assay of serum PSA, is currently under evaluation [6]. However, in the setting where a major goal of chemotherapy is palliation, reduction of PSA levels may not correlate with changes in quality of life [21]. Tannock and associates have shown that baseline measures of performance status, pain score and well-being correlate more closely with survival than does PSA fluctuation [21]. Other studies have also indicated that there may be little correlation between PSA change and symptomatic response or survival [22].

In addition to the assessment of response, difficulties often arise in the interpretation of the survival figures documented after a specific treatment as many patients receive a series of agents over a prolonged time interval as a result of series of relapses. It may, therefore, be difficult to attribute a survival benefit to a particular drug. In the past, because of the lack of suitable indices of response, many reports applied survival figures (often in a non-randomised manner) as indicators of specific patient benefit from chemotherapy [23]. However, this may have been an important error as patients with stable disease may live longer because of the more indolent nature of their disease rather than due to the effects of chemotherapy [3–5].

The median survival for hormone refractory prostate cancer is only 6 months provided that true hormone resistance is demonstrated [3, 4]. In many patients with allegedly hormone-resistant disease, persistent production of androgens can be demonstrated [3]; this can reflect a residual fragment of functioning testicular tissue in the patient after bilateral orchiectomy, the production of androgenic steroids by the adrenal glands, or compliance problems with medications, such as oestrogens or luteinising hormone releasing hormone (LHRH) agonists. These causes of apparent, artefactual hormone resistance should be excluded before the patient is considered for treatment with cytotoxic or other systemic agents (Table 1). In the setting of true hormone resistance, the goals of therapy are predominantly palliative;

it is therefore important that chemotherapy, if used at this stage of the disease, should lead at least to symptom relief and improvement in quality of life. Elderly patients tend to be more conservative in their attitudes to risk-taking and to the issue of toxicity of treatment [24], and will often place a higher emphasis on palliative benefit than on a modest prolongation of life. The role of chemotherapy is also affected by the fact that the elderly patients with prostate cancer often suffer from a range of intercurrent medical disorders which may confound the assessment of benefit, toxicity and survival [25], especially in smaller and non-randomised series. These factors limit the choice of agents available for treatment.

The stringency of the criteria of assessment that are applied can have a substantial impact on the reported outcome of phase II trials [26, 27]. For example, Yagoda and associates reported responses to cisplatin ranging from 4 to 20%, depending upon the criteria of assessment [26] and an even wider range of apparent activity has also been demonstrated for mitoxantrone [27]. These vagaries of assessment and the innate heterogeneity of both the tumours and the patient population have somewhat inhibited the application of chemotherapy to the management of this disease.

CONVENTIONAL CYTOTOXIC AGENTS

For several decades, it has been known that single agent chemotherapy can achieve some measure of tumour shrinkage when used against carcinoma of the prostate, as reviewed in detail previously [3, 4]. The activity of established cytotoxic agents is summarised in Table 2. Although combination chemotherapy regimens often yield higher objective response rates, these do not appear to correlate with improved survival or quality of life, and no randomised trials have convincingly demonstrated the superiority of combination chemotherapy to date [3, 4]. In fact, in many instances, combination regimens are only associated with enhanced toxicity.

Alkylating agents

Of the established agents, it is our view that cyclophosphamide remains one of the most useful, based on its relatively mild profile of toxicity, the (somewhat flawed) randomised data published by the National Prostatic Cancer Project [28], our own experience with its application as an oral formulation [19] and its relatively modest cost, when compared to many other agents. When administered as an oral dose of 100 mg/m^2/day for 14 days to patients with metastatic, hormone refractory disease, we noted a subjective improvement in 18 of 30 patients (60%), and an objective partial response rate of 20%, using the NPCP criteria of response. In this series, the toxicity was modest, with mild myelosuppression predominating [19]. In a later study, a PSA response rate of 30% was documented in a similar cohort of cases [29]. An extension of the attempt to use this non-toxic oral regimen has been the addition of a 14-day schedule of oral etoposide, which may add to the objective response rate [30], although these approaches have not been compared in a randomised study. At the other end of the spectrum, parenteral cyclophosphamide has been assessed at doses as high as 4.5 g/m^2, yielding equivalent antitumour effects at the expense of considerably more toxicity [31, 32]. To date, no published randomised studies have supported the role of dose intensity in the treatment of prostate cancer. Perhaps of more interest has been an innovative approach to biochemical modulation of alkylating agent therapy. For example, N,N-diethyl-2-[4-(phenylmethyl)phenoxy]ethamine (DPPE), an intracellular histamine antagonist, appears to increase the response rate of hormone refractory prostate cancer to treatment with parenteral cyclophosphamide [33]. Brandes and colleagues have reported a study in which partial remissions were observed in 5 of 7 patients with measurable soft tissue disease, also noting one complete response and two partial remissions among 16 patients with osseous metastases [33], and 85% of patients with bone pain showed an improvement.

The early experience with other alkylating agents, such as ifosfamide, has not been especially encouraging [34], and

Table 2. Cytotoxic agents active against prostate cancer

Drug class	Agents	Objective response	Major symptom response
Anthracyclines	Doxorubicin	10–20%	Yes
	Mitoxantrone	10–20%	Yes
	Epirubicin	10–20%	?
Alkylating agents	Cyclophosphamide	10–20%	Yes
	CCNU	10–20%	?
	Ifosfamide	10–20%	?
Vinca alkaloids	Vinblastine	10–20%	?
	Vincristine	<10%	No
	Navelbine	10–20%	?
Antibiotics	Mitomycin	10–20%	Yes
Spindle inhibitors	Estramustine phosphate	10–20%	Yes
	Paclitaxel	<10%	No
Platinum complexes	Cisplatin	10–20%	?
	Carboplatin	<10%	No?
Antimetabolites	Methotrexate	10–20%	No?
	5-fluorouracil	<10%	No?
Topoisomerase inhibitors	Etoposide	<10%	No
	Topotecan	<10%	?

Randomised trials have not demonstrated a survival benefit or improved quality of life from combination chemotherapy regimens, despite higher objective response rates.

randomised trials comparing single agent alkylating agents against alkylating agents in combination regimens have not shown any difference in survival, but usually an increased level of toxicity [35, 36].

Anthracycline antibiotics and analogues

Also of clinical importance, the anthracycline antibiotics have been applied extensively to the management of advanced prostate cancer, including a weekly schedule of doxorubicin at a dose of 20 mg/m^2/week [37] and a 3-weekly regimen at 30–50 mg/m^2 [38]. Response rates have varied from 5 to 84%, with higher response rates tending to occur with the low-dose weekly schedule. A combination of weekly doxorubicin (20 mg/m^2) with prednisone (5 mg, twice daily by mouth) was shown to be more effective (56% subjective response rate) than prednisone alone (23% response rate), but without a significant difference in survival [39]. Other anthracyclines tested include esorubicin and epirubicin. In a study of 77 evaluable patients, with weekly doses of 30 and 40 mg/m^2, respectively, partial response rates of 7% and 17% were reported, with disease stabilisation in 27% and 25%, respectively [40]. Idarubicin at a weekly dose of 30 mg/m^2 has also been shown to have limited value with partial remissions in 9% [41]. Weekly epirubicin at a dose of 30 mg/m^2 has a similar response rate to weekly doxorubicin at a dose of 25 mg/m^2, although it has been suggested that the cardiotoxicity is less severe in this patient population [42].

Mitoxantrone, an anthraquinone derivative that structurally resembles doxorubicin, has also been widely used in view of its moderate toxicity profile. Although Osbourne and associates demonstrated little activity in a cohort of previously treated patients [43], we reported considerable symptomatic benefit in a series of 50 cases with hormone refractory disease that had not previously received cytotoxics [27, 44], as well as an objective response rate in the range of 0–30%, depending upon the criteria of response that were employed. In a study using continuous infusion 1.0–1.5 mg/m^2/day for 14 days, repeated in a 28 day cycle, there was also clear evidence of symptomatic and objective benefit, confirmed by PSA responses [45]. Similarly, at a bolus dosing schedule of 3–4 mg/m^2/week, a partial remission rate of 7% and 29% disease stabilisation has been reported [46]. However, it was the pivotal study of Tannock and associates [21], in which the regimen of mitoxantrone plus prednisone was compared with prednisone alone, which resulted in the recent approval for the indication of hormone refractory prostate cancer by the U.S. Federal Drug Administration. In this study, clear evidence of improved quality of life (including reduced pain and improved performance status) was demonstrated for the patients receiving chemotherapy, although there was no evidence of survival benefit (perhaps because this study had a crossover design).

Platinum complexes

Most of the classes of cytotoxic agents have been tested against hormone refractory prostate cancer, but none has found a role as a standard of therapy. The platinum complexes have been studied extensively. Although the parent compound, cis-diammine dichloroplatinum II (cisplatin) has shown some evidence of activity [26], its profile of toxicity has limited its use amongst this patient population, although the introduction of the H2-blockers has changed this situation somewhat. Cisplatin-based combination regimens have occasionally been shown to yield high objective response rates [47, 48], but survival benefit has not been proven in randomised trials. Carboplatin, selected because of its improved profile of side-effects, has also not proven to be very effective in prostate cancer—for example, phase 2 studies in 29 patients with prostate cancer at doses ranging from 250–400 mg/m^2 have demonstrated an objective response rate of only 7% [49], although these data did not focus on subjective changes or PSA fluctuations. The use of isopropyl platinum, another analogue, has not been more effective than cisplatin or carboplatin [50].

Antimetabolites

5-Fluorouracil was one of the first cytotoxics to be used in prostate cancer. An objective response rate of 12% was reported by the NPCP, and if stable disease is considered to reflect patient benefit, overall improvement was seen in up to 36% [51]. A wide range of doses and treatment schedules has been reported, including daily and weekly boluses and continuous infusion, without any obvious difference in response rates [52, 53]. Other agents have been combined with 5-FU, including doxorubicin [54], doxorubicin plus mitomycin C [55] and cisplatin [56] in non-randomised trials that have been difficult to interpret with respect to ultimate clinical benefit. However, it has been suggested that the combination of 5-FU, doxorubicin and mitomycin C may produce a higher response rate than parenteral cyclophosphamide alone, although survival benefit was not addressed in this report [57]. Biochemical modulation of 5-FU by calcium leucovorin has not produced any notable benefit. Other antimetabolites, such as methotrexate [58], have not shown themselves to be especially useful against this disease.

Mitotic inhibitors

Vincristine appears to have only marginal activity in this disease [59], whereas vinblastine and vindesine both have apparent activity in up to 20% of cases [60, 61]. Navelbine, a novel synthetic vinca alkaloid (with the substitution of an 8-member ring structure with a 9-member ring in the catharanthine position of the molecule, which accounts for preferential binding to the mitotic microtubules and not the axonal microtubules) has also been tested against hormone refractory prostate cancer. A phase I/II study in 20 patients revealed a response rate of 30%, with a median improvement in PSA value of 31%; stable disease (of 2–7 months duration) was reported in 9/20 patients. Disease progression was noted in 3 patients at the time of reporting [62]. The true place of the vinca alkaloids has not been defined, although their modest toxicity profile and more recent studies with estramustine phosphate (now known to be a mitotic inhibitor) suggest that further assessment will be useful.

Estramustine is a unique compound consisting of an oestrogen compound linked by a carbamate ester to nitrogen mustard. The prodrug undergoes rapid dephosphorylation to estramustine and further metabolism to estrone. The advantage of this reaction is that its structure facilitates its entry into the prostate, with local release of the nitrogen mustard moiety into the prostate. However, of importance, its intracellular action has been shown to include inhibition of mitotic function [63], in contrast to the more conventional actions of alkylating agents. An overview of 18 phase

2 trials has reported a response rate of 37% in 634 patients, but this is reduced to 19% when the category of stable disease is excluded [64]. In our experience, the major problem has been poor gastro-intestinal tolerance, leading to poor compliance [65], and responses in hormone refractory disease have often been of relatively short duration [65, 66]. To some extent, the pattern of toxicity appears to be a function of dosage. More recently, based on its characteristic spindle inhibitory function, estramustine has been tested in combination with other inhibitors of mitosis, with apparently enhanced activity. Hudes and associates have carried out a phase II trial of vinblastine (6 mg/m^2/week) plus estramustine (140 mg orally every 8 h), with 50% of patients showing response as defined by a 50% reduction in circulating PSA levels [17]. While this is a promising approach, caution should be exercised in the interpretation of the data in view of the potential stage shift—i.e. the use of PSA response rather than more conventional indices. Other apparently active combinations have included the use of estramustine with etoposide [67], with paclitaxel [68] and with navelbine [69]. In each instance, subjective and objective improvements have been documented, accompanied by 50% reductions in PSA amplitude, but at the expense of gastrointestinal and bone marrow toxicity.

Miscellaneous

Mitomycin C alone has been reported to have an objective response rate of 21% in prostate cancer [70]. As noted above, it has been reported that the combination of cisplatin and mitomycin is active [47], with an objective response rate of 40% and a median survival of 15 months. Our experience has been that these agents will occasionally induce durable remissions in rapidly progressive, hormone-refractory disease that has previously been treated with cytotoxic agents, such as cyclophosphamide and mitoxantrone, but at the expense of considerable gastrointestinal and bone marrow toxicity (Javle and Raghavan, unpublished results).

The nitrosoureas, which function predominantly as alkylating agents, were extensively tested in the era prior to the introduction of measures of quality of life and PSA as an index of response. Apparent antitumour activity was demonstrated for CCNU and methyl-CCNU as single agents [71, 72] and in combination [73]. These agents should be tested again, using more modern critera of assessment, as their true utility cannot be defined from the published data.

NOVEL CYTOTOXIC AND BIOLOGICAL AGENTS

Several new agents have recently become available for clinical trial use, and preliminary assessment of their activity against hormone refractory prostate cancer has been reported. In view of the activity of topoisomerase inhibitors against a variety of malignancies, the camptothecin analogues have been the object of intense scrutiny, and because of the apparent utility of spindle inhibition against this disease, the taxanes have also been the focus of particular attention.

Topoisomerase I inhibitors

Topotecan, a topoisomerase I inhibitor, damages DNA independent of the proliferation rate, suggesting, potentially, a greater level of activity against more slowly growing tumours, such as prostatic adenocarcinoma. A phase II trial completed in 34 patients, treated with 1.5 mg/m^2/day intravenously for 5 days every 3 weeks, revealed an overall response rate of 7.1% among 28 evaluated cases [74]. Of 15 patients with measurable soft tissue disease, there was 1 partial response and 1 minor response. Dose reduction was required in 9 patients. Thus, preliminary data suggest only limited activity with significant toxicity associated with topotecan in prostate cancer [74]. However, other agents in this class may be more promising, including the camptothecin analogues, such as GI147211 and GI149893, which are potent inhibitors of topoisomerase I and which have been shown to be 1.5–1.8 times more effective than topotecan in suppressing tumour growth in a xenograft model of human cancer [75].

Taxanes

As a single agent, paclitaxel has been disappointing in the management of hormone-refractory prostate cancer. At a dose of 135–170 mg/m^2, administered every 21 days, little activity was noted with only a 5% partial response rate, with myelosuppression as the dose-limiting factor [76]. However, as noted above, preclinical studies have shown promising activity when paclitaxel is combined with other spindle inhibitors against prostate cancer. The role of docetaxel has yet to be defined.

Biologically active agents

Mitoguazone is an inhibitor of ornithine metabolism, which reduces polyamine production. As polyamines are found in high levels in prostate cancer, it was thought that mitoguazone might inhibit prostate cancer growth, and phase II testing was initiated. Clinical trials have demonstrated reduction in soft tissue masses [77, 78], but the drug has not found a routine place in clinical management in view of the associated toxicity and the lack of sustained clinical benefit. However, several other polyamine inhibitors, such as diethyl norspermine, are in clinical development and may have useful application if they exert a greater anticancer effect, provided that their profile of toxicity can be regulated.

Inhibitors of angiogenesis, such as pentosan and linomide, have been shown effective in inhibiting the growth of prostate cancer cell lines *in vitro*, but clinical data have not yet been produced to test these concepts [79–81].

Although beyond the scope of this overview, several other biological approaches are currently being assessed, either preclinically or in early clinical trials. These include approaches directed to the inhibition of cell signalling pathways, such as those mediated by tyrosine kinases or involving the function of autocrine growth factors, including IGF (insulin-like growth factor) 1 and 2 and TGF-beta (transforming growth factor) [82–84], the induction of apoptosis [85] and/or differentiation [86, 87] and a broad range of treatments encompassed under the classifications of immunotherapy and gene therapy. Although the majority of early clinical trials involve the application of these approaches to patients with advanced refractory disease because of the speculative nature of the therapies concerned, it makes more sense for them to be evaluated in the clinical context of minimal tumour burden. Thus, innovative designs of clinical trials for such treatment approaches are needed in order to maximise the chance of identifying any anticancer effect.

ADJUVANT AND NEOADJUVANT CHEMOTHERAPY

The use of cytotoxic agents as adjuvant or neoadjuvant therapy for patients with locally extensive prostate cancer represents a rapidly changing field, well beyond the scope of this review, and has been discussed in detail recently [88].

It appears that neoadjuvant and adjuvant hormonal systemic therapy are at least associated with a disease-free survival benefit when added to definitive local treatment for locally advanced prostate cancer [89, 90]. However, to date, the role for the early initiation of systemic cytotoxic therapy is much less clear. Most controlled trials have failed to demonstrate any significant overall survival benefit from the use of initial or adjuvant cytotoxic chemotherapy in addition to local treatment [88, 91–93]. However, it has been suggested that a disease-free survival benefit may be afforded in this setting [92, 93], although the design and analysis of these trials has been questioned. A controlled clinical trial is currently evaluating the utility of adjuvant systemic therapy for high risk prostate cancer that has been treated by radiotherapy [94].

CHEMO-ENDOCRINE THERAPY

The use of a combination of cytotoxic agents and hormones for the management of advanced prostate cancer has a sound theoretical basis, providing a broader coverage for the heterogeneous component cell populations. Preliminary clinical trials have been encouraging [95, 97], but randomised clinical trials have not shown any overall survival benefit from this approach, whether applied as neoadjuvant or adjuvant therapy [98]

TREATMENT OF VARIANTS OF PROSTATE CANCER

There is no established optimal treatment for the non-adenocarcinomatous variants of prostate cancer [99]. The reported treatment regimens used for small cell cancers of the prostate have been similar to those in small cell carcinoma of the lung, including etoposide, cisplatin, cyclophosphamide, vincristine and doxorubicin, with a response rate of approximately 60% [11, 12]. Despite a high response rate, the median survival of these patients is only 6–9 months. It may prove to be important for this variant to be recognised early by the pathologist, so that cytotoxic chemotherapy can be employed at an earlier stage, by analogy to bronchogenic small cell undifferentiated cancer.

In the case of transitional cell carcinoma of the prostate, there is an emerging recognition that this may constitute two separate entities: (a) cases which represent the growth of transitional cell carcinoma locally, which has arisen from the prostatic urethra; and (b) cases in which bladder cancer has penetrated full thickness, extending into the prostatic stroma [100]. Although the former type is associated with a better prognosis when presenting with clinically localised disease, there is no evidence that the outcome differs when the cancer is at an advanced or metastatic stage. The approach to the management of advanced or metastatic transitional cell cancer of the prostate has been very similar to that applied to locally advanced or metastatic transitional cell bladder cancer, predicated predominantly on combination chemotherapy regimens that include cisplatin, methotrexate, a vinca alkaloid and doxorubicin [101]. There has been no evidence that the response rate to chemotherapy for TCC of the prostate differs from that found in urothelial TCC, although there has been little in the published literature that relates specifically to the management of metastatic transitional cell cancer of the prostate *per se*.

CONCLUSION

After nearly half a century of application, the role of cytotoxic chemotherapy for prostate cancer remains controversial and uncertain. Increasing precision of assessment has led to the conclusion that the quality of life of patients with metastatic hormone-refractory prostate cancer may be improved by the judicious administration of cytotoxics, provided that care is taken to ensure a balance between activity and toxicity. The use of serial assessment of blood PSA levels has allowed a clearer definition of anticancer activity within the classification formerly known as 'disease stabilisation', although the ultimate biological significance of PSA response remains somewhat controversial.

The improved understanding of the heterogeneity of prostate cancer and of its complex molecular biology will allow the design and implementation of more rational clinical trials of chemotherapy for this disease. This, in turn, should lead to the correct use of this modality for the treatment of prostate cancer within the first decade of the next millennium.

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