The role of chemotherapy in advanced prostate cancer

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The development of hormone resistance is an unfortunate final common pathway in most patients with advanced prostate cancer, resulting in a narrowing of therapeutic options for the clinician, and limited median survival of 10–12 months for the patient. While cytotoxic chemotherapy has been utilized for many years, its efficacy has been disappointing. Quality of life assessments are increasingly used in assessing response in hormone-resistant prostate cancer (HRPC), and PSA has emerged as an important surrogate marker of response in both local and advanced disease. Estramustine and the taxanes have been investigated, as monotherapy and in combination, in the treatment of HRPC in phase 2 and 3 clinical trials, a number of which are ongoing. Substantial advances in the management of HRPC over the past decade have led to renewed optimism that improvement in survival can be achieved, and support the belief that chemotherapy plays a role in this pursuit. In tandem with the development of new agents, refined means of assessing response have been developed, and represent a key component of new research strategies in HRPC.

Key Words: hormone resistance, prostate cancer, chemotherapy

Introduction

The development of hormone resistance in patients with advanced prostate cancer is an unfortunate final common pathway for most.[1] The transformation results from a number of different processes resulting in progressive clinical disease despite adequate androgen suppression, usually after a median time of 2 years.[2] For the clinician, the number of potential therapeutic options narrows. For the patient, irrespective of the interventions, the median survival is limited to 10–12 months.[3]

Cytotoxic chemotherapy has been utilized for many years, and efficacy, as measured by tumor response, progression free survival, or overall survival, has been disappointing. A multiplicity of

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agents with a wide spectrum of antiproliferative mechanisms of action have been utilized. Maximum tumor response rates of 15%–20% have been observed in phase 2 testing Table 1. However, assessment of response in advanced prostate cancer has been hampered by the relative infrequency of measurable disease to which standard assessments of tumor response can be applied. Unlike many other solid tumors, metastasis tend to be predominantly osseous. If only patients with bidimensionally measurable disease were included in studies, only 20%–30% of prostate cancer patients would be eligible.[4]

Assessment of response

Clinical response has been increasingly accepted as alternate means of assessing efficacy in hormone-resistant prostate cancer (HRPC). In 1996, Tannock and colleagues reported on a randomized controlled study of the anthracenedione, mitoxantrone, in combination with low dose prednisone versus prednisone alone. The primary endpoint of the trial was palliative response, which utilizes both patient symptom scores and analgesic requirements. The palliative response rate for the mitoxantrone arm was 29%; median survival was 9 months for both arms.[5] A similar randomized trial conducted by the Cancer and Leukemia Group B (CALGB 9132) utilized survival as the primary endpoint and found no difference in either arm.[6] However, in the quality of life assessments, pain was improved with the chemotherapy. On the basis of these findings of clinical response in the two studies, the US Food and Drug Administration approved mitoxantrone for use in HRPC.[7] The mitoxantrone/prednisone combination remains the standard to which newer combinations are often compared. Quality-of-life assessments are increasingly an integral part of the assessment of response in HRPC.

Prostate-specific antigen (PSA) has also emerged as an important surrogate marker of response in both local and advanced disease. Changes in PSA appear to correlate to clinical outcome in patients treated with surgery, radiation therapy, and antiandrogens.[8-10] Similarly, in HRPC, PSA declines tend to reflect clinical response, but not absolutely.[11] In the Tannock study, 48% of patients achieving a palliative response had a corresponding ≥ 50% reduction in PSA, whereas only 21% of patients who did not experience a palliative response had a ≥ 50% reduction in PSA.[5] PSA responses have been variably defined in clinical trials, and these discrepancies have impaired the interpretation and subsequent development of new agents. In 1999, the PSA Working Group, upon consensus, outlined definitions for PSA response for Phase 2 clinical trials.[12] Although PSA response does not meet the criterion for a surrogate of survival, it remains an important parameter by which agents can be assessed prior to further evaluation in the phase 3 setting.

Baseline PSA levels have been variably shown to connote prognosis in HRPC.[11,13] Other more consistently reported prognostic factors include performance status, baseline hemoglobin, and alkaline phosphatase.[14,15] Consequently, in assessments and certainly in comparisons of new agents, these prognostic factors should be appropriately reported or controlled to more accurately evaluate outcome.

TABLE 1. **Single agents in prostate cancer**

Class	Agent	Response rate
Anthracyclines	Doxorubicin	10%-20%
	Mitoxantrone	10%-20%
Alkylating Agents	Cyclophosphamide	10%-20%
	CCNU	10%-20%
Vinca Alkaloid	Vinblastine	10%-20%
Taxanes	Paclitaxel	10%-20%
	Docetaxel	25%-40%
Antimicrotubule	Estramustine	5%-20%
Topo-isomerase inhibitors	Etoposide	<10%

Estramustine combinations

Estramustine is an oral agent composed of a stable conjugate of nornitrogen mustard and estradiol, and has been in clinical use for more than twenty years.[16] It was initially thought that the estrogenic component bound to steroid receptors and that the nitrogen mustard, when released intracellularly, caused DNA alkylation. However, more recent studies have indicated that the cytotoxic effect is mediated through estramustine's depolymerization of cytoplasmic microtubules and microfilaments.[17] As a single agent, response rates with estramustine have been low, and have only been observed at relatively high doses with considerable toxicity, namely nausea/vomiting, fluid retention, and thromboembolism.[18] When used *in vitro* in combination with other anti-tubule agents such as the vinca alkyloids and taxanes, anti-tumor activity appeared to be enhanced. Reduced doses of estramustine could subsequently be utilized with

TABLE 2. **Select phase II trials of Estramustine(E) in combination**

Author	Treatment	Patients (#)	Measurable disease response (%)	≥50% PSA (%)
Hudes 1992[19]	E + Vinblastine	25	14	61
Dimopoulos 1997[20]	E + Etoposide	56	45	58
Petrylak 1999[21]	E + Docetaxel	34	28	63
Hudes 1997[22]	E + Paclitaxel	35	57	74
Savarese 1999[23]	E + Docetaxel + Hydrocortisone	40	23	69
Smith 1999[24]	E + Etoposide + Paclitaxel	37	45	65
Kelly 2000[25]	E + Paclitaxel + Carboplatin	26	64	73

improved effectiveness and with potentially lessened toxicity. Consequently, a wide variety of phase II clinical trials have examined combinations of estramustine in HRPC Table 2.[19–25] In a Phase 3 study of estramustine combined with vinblastine versus vinblastine alone, Hudes et al reported that PSA response was superior with the combination (25.2% versus 3.2%), and that time to progression was also enhanced.[26] Compliance with pain and quality of life assessments was low (23%) and therefore symptomatic responses could not be adequately addressed. Surprisingly, grade 3 or 4 granulocytopenia was seen more commonly in the vinblastine alone arm, whereas grade 2 or greater nausea was significantly more frequent in the combination arm (27% versus 7%). In an EORTC phase 3 trial of estramustine and vinblastine versus estramustine alone, toxicity was excessive and PSA response rates were low at 37% and 31%, respectively.[27]

Docetaxel combinations

The Taxanes have been shown *in vitro* to disrupt the intracellular microtubule network in prostate cancer cell lines. In particular, docetaxel induces Bcl-2 phosphorylation and consequently inhibits the antiapoptotic effects of Bcl-2.[28] Single agent docetaxel has undergone limited phase 2 testing, with PSA response rates ranging from 30%-46% Table 3.[29–32]

TABLE 3. **Select phase II trials of Docetaxel (D)**

Treatment	Author	Patients (%)	Measurable disease response (%)	≥ 50% PSA response (%)
D 75 mg/m^{2}Q21d	Picus (1999)[29]	35	28	46
D 75 mg/m^{2}Q21d	Friedland (1999)[30]	21	60	38
D 36 mg/m^2/wk x 6	Berry (1999)[31]	60	33	34
D 36 mg/m^2/wk x 6	Beer (2000)[32]	25	N	43

With the potential for synergistic mechanisms of action, docetaxel and estramustine have been explored in phase 1 and 2 clinical trials. In a study by Petrylak and colleagues, the combination was generally well-tolerated and resulted in a ≥ 50% PSA reduction in 50% of extensively pre-treated patients.[33] Among patients with soft tissue disease, the objective response rate was 28%. Although the patients were highly selected, the median survival was 23 months. The incidence of thromboembolism among the total of 121 patients who received the combination was 11%, and is similar to rates previously seen in studies involving high-dose, single agent estramustine. The thromboembolism incidence may be potentially modified using lower estramustine doses. The Southwest Oncology Group (SWOG 9916) have initiated a phase 3 trial comparing docetaxel/estramustine with mitoxantrone/prednisone. The primary endpoint is survival. Additionally, Aventis Pharma (TAX327) has embarked on a large international trial of intermittent docetaxel versus weekly docetaxel versus mitoxantrone in HRPC. This trial also is designed with survival as the primary endpoint, but secondary endpoints include clinical response, quality of life, and PSA response. Depending upon the rate of events, the results should be available in 2003.

Neoadjuvant chemotherapy

An important cohort of patients present with apparent organ-confined disease; however, they ultimately progress to extra-prostatic extension or occult metastatic disease.[34] Stage, baseline PSA and Gleason score have been widely recognized as important prognostic variables which can identify patients at higher risk for local or systemic relapse.[35] With the development of more active cytotoxic agents, the early use of chemotherapy is being explored in order to potentially reduce risk of late relapse. Neoadjuvant trials of hormonal treatment and chemotherapy in high-risk patients are currently being conducted.[36] Determination of prostate tumor response can be conducted prior to definitive local therapy such as radical prostatectomy or radiotherapy. Pettaway and colleagues reported on a phase 1–2 trial of neoadjuvant androgen ablation, ketoconazole, doxorubicin, vinblastine, and estramustine (KAVE) in 33 patients with high-risk localized prostate cancer prior to radical prostatectomy.[37] Of the 17 patients with clinical T3 disease, only 3 (18%) were downstaged to pT2, and no patients were downstaged to pT0. Nevertheless, the neoadjuvant therapy was tolerated reasonably well and there were no intraoperative complications. In Canada, two trials evaluating the combination of antiandrogens with docetaxel prior to prostatectomy or radical radiotherapy are being conducted.

Conclusions

Although the management of HRPC was once felt to be nihilistic, substantial advances over the past decade have led to renewed optimism. Improvement in survival remains the goal of ongoing research initiatives, and chemotherapy appears to have a role in this pursuit. Alongside the development of newer cytotoxic agents has come the establishment of additional means to evaluate response. Clinical parameters of response are becoming an integral component of new research strategies. Furthermore, an increased recognition regarding the quality of the survival improvement represents a welcome change in the management of patients with advanced prostate cancer. □

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