

Hormone Refractory Prostate Cancer

Background

Hormone Refractory Prostate Cancer (HRPC) is defined as the progression of disease in the presence of castrate serum levels of testosterone. HRPC remains a lethal disease and represents a significant unmet medical need:

- prostate cancer is the most common cancer in US males and is the second leading cause of cancer deaths in US men
- deaths are due to progressive metastatic disease related to failed initial therapies
- there were over 180,000 new cases and 42,000 deaths reported in the US in the year 2000 (*American Cancer Society (SEER), 1996-2000*)
- 10-50% of patients with localized disease will progress to advanced disease
- hormone therapy is currently the standard of care for advanced stage prostate cancer patients
- 80% of patients with advanced disease respond to primary hormonal manipulation (medical or surgical testicular ablation)
- median length of response to hormone therapy is 18 to 24 months; most if not all patients subsequently relapse
- prognosis for patients showing rising prostate specific antigen (PSA) or other signs of progression at this stage is poor with only 60% surviving another year.
- patients with advanced disease suffer from many complications including severe bone pain
- most patients will die of HRPC within 2 years of diagnosed disease progression

Stages and Incidents of Disease, Progression and Deaths

Frequency of patients presenting at each stage of disease has changed remarkably with introduction of the PSA screening in the early 1990's. Estimates from the 1995 National Cancer Database is as follows: 25% with Stage I (A= local disease), 56% with Stage II (B = palpable but confined to the prostate), 13% Stage III (C = spread regionally but without evidence of metastasis), and 10% Stage IV (D = metastatic disease).

Surgery and radiation therapy are the standards of care in Stage I and II patients. When prostate cancer becomes locally aggressive (Stage III) radiation and hormone therapy (GNRH agonists/antagonists) become the major approaches. Patients with metastatic disease are treated with hormone therapy until they become resistant. At this point, patients (HRPC) may be treated with chemotherapy. Chemotherapy treatment of HRPC patients has been generally ineffective and patients generally do not survive more than 12-18 months.

	Localized		Advanced Disease		
Stage	Stage I (A1)	Stage II (A2, B1 or B2)	Stage III (C)	Stage IV (D1 or D2)	Deaths in 2000
Description	Clinically inapparent tumor not palpable or visible by imaging	Tumor confined to prostate	Tumor extends outside prostate capsule	Tumor invades surrounding structures (bladder, rectum, etc)	
Newly Diagnosed Cases in 1999					
US	45,900	92,700	24,300	19,900	35,882
5 European	20,200	46,800	29,000	19,700	53,335
Japan	4,400	6,400	1,600	700	6,913
Number of Prevalent Cases in 1999					
US	229,400	377,100	165,400	175,900	
5 European	85,700	167,200	128,600	128,700	
Japan	19,600	23,800	10,100	8,400	
Five- year	79-99%	68-99%	40-93%	20-81%	
Treatment	Surgery or Radiotherapy	Surgery, Radiotherapy or Brachytherapy	Radiation, Hormone therapy, Surgery, Chemotherapy or Brachytherapy	Hormone Therapy or Chemotherapy	

Sources: Angiogenesis Inhibition in Cancer Therapy, Onkos Study #47, May 2000 Decision Resources Inc. Prostate Cancer, Onkos Study #47, May 2001 Decision Resources Inc. Ferlay, F. Bray, P. Pisani and D.M. Parkin. GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. IARC Cancer Base No. 5. Lyon, IARC Press, 2001

Current Treatment Options in HRPC

The standard of treatment for advanced disease consists of hormone therapy. Most initially respond to this treatment however, signs of disease progression appear after 18 to 24 months. Median survival for patients with rising PSA is 12 to 18 months. For patients failing hormone therapy options currently include: secondary hormone therapy, chemotherapy, radiotherapy, growth factor inhibitors and other biologic agents. Chemotherapy is typically given to patients who are refractory to hormone therapy as a second or third line treatment.

Currently approved agents include:

Novantron (Mitoxantrone) – Immunex

Approved Indication: Novantrone in combination with cortecosteroid prednisone is indicated as initial chemotherapy for the treatment of patients with pain related to advanced HRPC.

- Primary endpoint: primary palliation response
- Secondary endpoint: survival, lesion size change, PSA level decline, Quality of Life (QOL)
- Randomized studies: Nov. + Prednisone vs. Prednisone and Nov. + Hydrocortisone vs. Hydrocortisone

Novantrone Phase 2 results:

I) HRPC Phase 2a trial: n=27

Efficacy results: 1 partial responder (based on 50% decrease in tumor size) and 12 patients with stable disease, 9 patients had palliative responses with decreased pain intensity/analgesic use

II) HRPC Phase 2b trial: n=161

Novantrone + prednisone vs. prednisone alone

Efficacy results: 29% in N+P arm met primary palliative response vs. 12% in P arm (p=0.011). PSA fall of 50% or greater for 2 follow up assessments (consecutive) occurred in 33% of patients in the N+P arm and median survival in this arm was 11 months.

III) Cancer And Leukemia Group B study: n=242 in HRPC patients

Novantrone + Hydrocortisone vs. Hydrocortisone alone

Efficacy results: No survival differences in either arm. Median survival was 11 months using the National Prostate Cancer Protocol (NPCP) criteria; Partial Responses (PR) were 8% in N+H arm, 1.6% in H alone arm.

Emcyt (Estramustine phosphate) – Pharmacia

Approved Indication: Emcyt capsules are indicated in the palliative treatment of patients with metastatic and/or progressive carcinoma of the prostate.

- Primary endpoint: overall and progression-free survival
- Secondary endpoint: lesion size change, QOL
- Randomized studies: Emcyt vs. DES and Emcyt + surgery vs. surgery

Overview AMD-473: A potential new therapeutic option in HRPC

Compared to other agents used in HRPC during phase II, AMD-473 has favorable results (28%), which will enable the clinical development plan of AMD-473 to move forward with a target profile use in potentially HRPC and Prostate Cancer. In Phase II single agent trials, using reduction in lesion size as the response criteria, Cisplatin and Carboplatin achieved less than 20% response rate. An Oxaliplatin phase II study demonstrated no response in HRPC. A phase II study with an oral platinum compound (Satraplatin) achieved a response in 1 out of 9 patients. Estramustine studies in phase III had less than 10% of the patients responding. A combination trial of Novantrone and Prednisone showed about 8% of the patients with a positive response.

AMD-473 Comparators

Direct comparison is difficult at this stage of development due to differences in trial endpoints, trial design, patient recruitment, and trial center protocols. Relevant comparators for AMD-473 include:

- Novantrone, the most recently approved treatment option
- other platinum, widely accepted agents in the same class
- Taxotere, a compound in phase III HRPC trials

Please Refer to Tables on the next two pages which provide a breakdown of clinical trials for Cisplatin Trials 1979,1983,1999 and Carboplatin Trials 1990, 1993, 1995, 1998; Taxotere Trials

Agent	Year	N*	Dosing	RR in lesion size reduction (reduction of 30% or 50%)		PSA drop (>50% or >80%)		RR in QOL/bone pain/clinical status	Stable disease	Survival	TTP	Source
				Reduction of 30%	Reduction of 50%	≥ 50%	> 80%					
Cisplatin	1979	45	1 mg/kg once per week for the first 6 wks and every 3 wks thereafter		PR: 13 out of 45, 29%	NA	NA	18 out of 45, 40%	6 out of 45, 13%		6 m	<i>Urology</i> 1979, 13(3), 267
Cisplatin	1979	54	1 mg/kg once per week for the first 6 wks and every 3 wks thereafter		PR: 17 out of 54, 31.4%	NA	NA	NA	NA	NA	NA	<i>Cancer Treat. Reports</i> 1979, 63(9-10), 1579
Cisplatin	1979	21	75 mg/m ² every 3 wks		PR: 4 out of 21, 19%	NA	NA	NA	NA	NA	NA	<i>Cancer Treat. Reports</i> 1979, 63(9-10), 1557
Cisplatin	1979	25	50-70 mg/m ² every 3 wks, median cycles of 3		PR 3 out of 25, 12%	NA		NA	1 out of 25, 4%	53 weeks		<i>Cancer Treat. Reports</i> 1979, 44, 1553
Cisplatin	1983	43	60 mg/m ² every 3 wks		No response	NA	NA	16 out of 43, 36%	9 out of 43, 21%	NA	NA	<i>J. Urology</i> 1983, 129, 56
Cisplatin + Estramustine	1983	42	60 mg/m ² cisplatin every 3 wks + 200 mg/m ² estramustine 3 x per day		No response	NA	NA	18 out of 42, 44%	14 out of 42, 33%	NA	NA	<i>J. Urology</i> 1983, 129, 56
Cisplatin + Epirubicin	1999	21	Cisplatin at 80 mg.m ² + Epirubicin at 100 mg/m ²		14%	32%	NA	38%	48%	NA	NA	<i>Am. J. Clin. Oncol.</i> 1999, 22(5), 471
Carboplatin	1990	24	400 mg/m ²		PR: 1 out of 5	NA		PR: 4/24, 17%	NA	297 days	94 days	<i>Invest. New Drugs</i> 1990, 8, S91
Carboplatin	1993	12	150 mg/m ² weekly for at least 8 courses		PR: 2 out of 12, 17%	NA		NA	8 out of 12, 67%	NA	7 m	<i>Eur J. Cancer</i> 1993, 29A (15), 2094
Carboplatin	1995	35	150 mg/m ² weekly for at least 8 courses		PR: 6 out of 35, 17%	10 out of 35, 28%		NA	10 out of 35, 28%	10 m	NA	<i>Anticancer Res</i> 1995, 15, 2825
Carboplatin	1998	17	400 mg/m ² every 28 d		PR: 1 out of 17, 6%			13 out of 27, 48%	9 out of 17, 53%	NA	NA	<i>Support Care Cancer</i> 1998, 6, 462
Etoposide + Epirubicin + Carboplatin	1996	12	Etoposide at 30 mg/m ² + Carboplatin at 150 mg.m ² + Epirubicin at 30 mg/m ² for median cycles of 3		PR: 3 out of 12, 25%			4 out of 12, 33%	8 out of 12, 67%			<i>Int. Urology Nephrology</i> 1996, 28(1), 79-85
Oxaliplatin	2000	22	130 mg/m ² every 3 wks	NA	NA	2 out of 22, 8%	NA	NA	7 out of 22, 32%	NA	2.3 m	2000 ASCO Abstract 1415
JM-216, Satraplatin	1998	22	120 mg/m ² /d x 5 every 28 days		1 out of 9 patients, 11%	7 out of 22, 32%	6 out of 22, 27%	NA	NA	NA	NA	1998 ASCO Abstract 1210

Docetaxel (Taxotere) Single Agent Trials

Source	Trial	Measurable Response	PSA Drop	QOL
Berry, W. Dakhil BW, Gregurich MA, Asmar L. Seminar in Oncol 28(4) suppl 15 pp 8-15. Aug 2001	Phase II Demographics 97%(58) 2nd hormone of whom 20 (34%) progress during study 70% palliative radiation 27% mitixantrone	6 measurable 2/6 (33%) 1CR (Baseline PSA=0 due to undif. Tumor) 1PR	≥50% 24/60 (41%) duration 4.5mo ≥80% 16/60 (27%) duration 5.0 mo	Overall TTP 5.1 mo. 9 pts progress-free 18+mo TTP ≥50%: 6.6mo TTP ≤50%: 4.3 mo (p=0.01) Median survival: 9.4 mo Of 60 patients 37 (62%) died within 18mo Survival ≥50%: not reached Survival ≤50%: 8.1 mo Mc Gill Pain (n=37) 3PR (8%) 34 SD (92%) 84% of patients completing 3 cycles (1/2) filled out QOL survey- Qualitative improvement.
Driecer, R, Klein E. Seminar in Oncol 28(4) suppl 15 pp 45-48. Aug 2001	Phase II <u>Locally advanced disease</u> 13 patients enrolled target 28 6wk course 40mg/m ² every 7 days followed by radical prostatectomy (within 3 wk of chemo completion) End point pathologic CR		PSA reduction in 7/10 patients who completed 6-week course	

Docetaxel (Taxotere) Combination Agent Trials

Source	Trial	Measurable Response	PSA Drop	QOL
Decision Resources Report	Phase III-Underway SWOG-S9916 Docetaxel+Estramustine Vs. Mitoxantrone+prednisone	End Points: Overall survival and progression free survival	620 patients over 3.5 years	
Savarese DM J Clin Oncol 19(9) 2506-16 May 1 2001	Phase II Docetaxel+Estramustine+ Low Dose Hydrocortisone	Overall Resp. 12/24 (50%) • 3CR, (13%) • 9PR (38%) 50% tumor reduction and a 75% reduction in PSA	Total (N=44) Overall combined 54% ≥50% 30/44 (68%) ≥75% 25/44 (57%)	Median survival: 20 mo. TTP: 8 mo TTP measurable: 10mo. TTP assessable: 7Mo
Figg, WD, Arlen P, Gulley J et al. Seminar in. Oncol 28(4) suppl 15 pp 62-66. Aug 2001	Phase II Docetaxel Plus Thalidomide 59 patients enrolled (goal 75) 53 evaluable for response As of April 2001 trial open 16 mo		6/17 (35%) docetaxel alone had a PSA drop of ≥50% 19/36 (53%) combo had a PSA drop of ≥50%	
Small EJ, AntiCancer drugs 12 (suppl 1) S17-S20 2001	Review	Study Patients	PSA>50%(%)	Measurable disease(%)
		Savarese et al D+E 47	69	23
		Petryak et al. D+E 35	74	57
		Hudes et al. P+E 58	58	44

Common End Points in Prostate Cancer/Hormone Resistant Prostate Cancer Treatment

As with most cancers the ultimate test of efficacy is an improvement in overall survival and disease free survival. Some other common endpoints seen in HRPC trials include:

Measurable disease

- Measure of physical tumor shrinkage using either RECIST or WHO criteria
- Most HRPC metastases are to the bone limiting the number of patients with measurable disease

PSA – prostate specific antigen

- Biochemical marker level commonly used to evaluate patient response
- Decreases in serum levels of PSA of $\geq 50\%$ or $\geq 80\%$ are commonly used measure of response
- Debate exists as to accuracy of the measure and the correlation with prognostic improvement

Quality of Life

- Measurements of decreases in level of pain, or decreases in opiate use
- Somewhat subjective and difficult to compare between different trials

End point measurements have changed:

Response Evaluation Criteria in Solid Tumors (RECIST)

In 1981, most investigators around the world adopted the World Health Organization (WHO) criteria for evaluating objective tumor response. However, problems developed over the years as institutions made different modifications or clarifications to the WHO criteria, resulting in a situation where comparison of results between organizations has become increasingly difficult. To address this problem, WHO, The National Cancer Institute (NCI), and the European Organization for Research and Treatment of Cancer (EORTC) have recently adopted the Response Evaluation Criteria in Solid Tumors (RECIST). While the new RECIST response criteria are designed to replace the existing WHO criteria, they were also designed to maintain comparability with them. The RECIST measurements are based on unidimensional measurements of tumor diameters whereas the WHO criteria were based on the product of bidimensional measurements of the tumor. Based on retrospective statistical evaluation of 14 trials no statistical difference in response was seen between the 2 criteria. Comparability of the two methods is shown in the following chart.

Relationship between change in diameter and product for WHO and RECIST Criteria:

	WHO Product [(2r ²)]	RECIST diameter (2r)
Response	Decrease	Decrease
	50%	30%
Disease Progression	Increase	Increase
Progressive Disease (PD)	25%	20%
Padhani, AR and Ollivier L. The RECIST criteria: implications for diagnostic radiologists. The British Journal of Radiology, 74(2001), 983-986.pg 984		

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