Original Article
Middle East Journal of Cancer 2012; 3(4): 101-108

The Effect of Multiplicity of Metastatic Sites on Hormone Refractory Prostate Cancer

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Abstract

Background: This study retrospectively evaluated the prognostic factors and treatment outcome of patients with hormone-refractory prostate cancer who received chemotherapy.

Methods: We reviewed records of hormone-refractory prostate cancer patients who received chemotherapy between December 2004 and May 2011 at the Clinical Oncology and Nuclear Medicine Department, Mansoura University and the Oncology Outpatient Clinic of East Delta Insurance Institute, Egypt with regards to patient characteristics, response to chemotherapy, toxicity, survival and prognostic factors.

Results: A total of 37 records were analyzed. Patients' median age was 66 years. The majority (70%) had bone metastases. One patient received single agent prednisolone and 2 received single agent vinorelbine. There were 34 (92%) who received a docetaxel-based chemotherapy regimen for whom we determined the treatment outcome and prognostic factors. Patients underwent a median of six cycles of treatment (range: 4–11). Fourteen of 34 patients (%41) had ≥50% decrease in serum prostatic-surface antigen. Among 16 patients who had measurable disease at the baseline, 8 (50%) achieved a partial response according to radiographic criteria. Of the 25 patients who experienced cancer pain before treatment initiation, 15 (60%) reduced their analgesic drug intake. Grades 3-4 neutropenia occurred in 13 (38%) patients. The median follow-up period was 13 months and the median event-free survival was 7 months (range: 4-31). The median overall survival period was 12 months (range: 4.5-37). According to multivariate regression analysis, multiplicity of metastatic sites was the only independent prognostic factor (P=0.005).

Conclusions: Hormone-refractory prostate cancer is not considered totally resistant to chemotherapy. In this study, multiplicity of metastatic sites is the only independent prognostic factor. Survival figures are not satisfactory, therefore additional research is needed for achieving a better treatment outcome.

Keywords: Prostate cancer, Chemotherapy, Docetaxel, Hormone refractory cancer, Corticosteroids

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Middle East Journal of Cancer

Received: July 1, 2012; Accepted: September 3, 2012

Introduction

In Egypt prostate cancer is uncommon. It represents 2% of all incident cancers, ranking seventh in males. The majority of cases (79%) present with advanced disease.[1]

Early-stage prostate cancer can be cured by radical surgery or radiation therapy. However, treatment of metastatic prostate cancer is palliative. Although most patients with metastatic disease initially respond to conventional androgen deprivation therapy with medical or surgical castration, the median duration of disease control is between 18 and 24 months.[2] However, prostate cancer eventually becomes refractory to hormone treatment (HT). There are some treatment options for patients with hormone refractory prostate cancer (HRPC), such as chemotherapy. In the late 1990s, the combination of mitoxantrone and corticosteroids have been shown to provide pain relief, improvements in prostate-specific antigen (PSA) levels and improvement in quality of life (QoL) compared with corticosteroid alone; however, there was no improvement in survival.[3]

Docetaxel has emerged as a promising agent because of its ability to stabilize tubulin and prevent dissociation of the mitotic spindle. Docetaxel also has the potential ability to counter the prosurvival effects of BCL-2, which has been found to be overexpressed in HRPC.[4] Docetaxel (75 mg/m^2) administered every three weeks as a single-agent treatment produced a 46% PSA RR; responses were maintained for a median of nine months.[5]

Interest in comparing docetaxel-based with mitoxantrone-based regimens has encouraged well-known phase III trials. In the TAX 327 phase III randomized trial, 1006 patients were divided into three groups: prednisone (5 mg, bid) in conjunction with: either docetaxel (75 mg/m^2, every three weeks), docetaxel (30 mg/m^2, weekly for five out of every six weeks) or mitoxantrone (12 mg/m^2, every three weeks). The median overall survival with 75 mg/m^2 docetaxel administered every three weeks (18.9 months) was statistically longer than with 12 mg/m^2 mitoxantrone every three weeks (16.5 months, P=0.009).[6] Thus, the combination of docetaxel and steroids were popularized as an effective treatment for HRPC in the US.

In the present study, we retrospectively reviewed records of HRPC patients in Egypt who received chemotherapy. Our intent was to evaluate the efficacy, toxicity, survival, and prognostic factors among HRPC patients.

Patients and Methods

We obtained Institutional Review Board approval for this retrospective study. Hospital records of patients with histologically proven metastatic HRPC who received chemotherapy between December 2004 and May 2011 at the Clinical Oncology and Nuclear Medicine Department of Mansoura University and the Oncology Outpatient Clinic of East Delta Insurance Institute, Egypt were reviewed. Analysis concentrated on patients' baseline characteristics, chemotherapy regimens, PSA response, objective response rate according to Response Evaluation Criteria in Solid Tumors (RECIST),[7] toxicity, prognostic factors, and survival. Pretreament assessments included complete history and physical examination, PSA levels, complete laboratory profile, chest X-ray, computed tomography scan of the abdomen and pelvis, and bone scan.

Chemotherapy was administered to patients who met the following criteria: Eastern

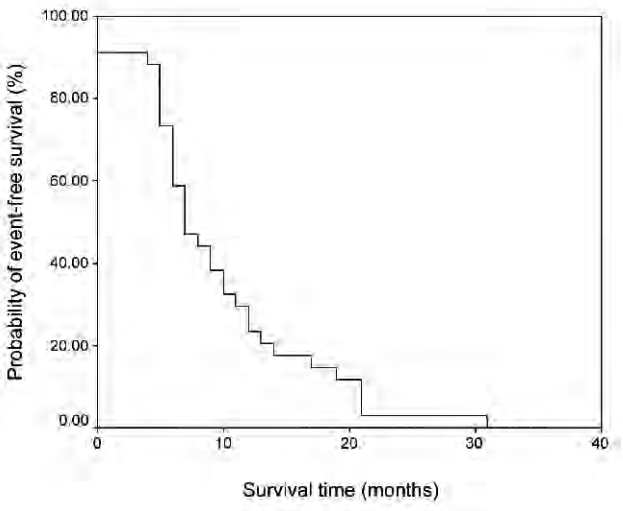

Figure 1. Event-free survival in months (n=34)

Cooperative Oncology Group (ECOG) performance status of 0-2; adequate baseline bone marrow function (neutrophil count ≥2000/mm^3 and platelet count ≥100000/mm^3); adequate hepatic function (total bilirubin level ≤1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase levels ≤1.5× the upper limit of normal); and adequate renal function (≤1.5× the upper limit of normal). Chlormadinone acetate or flutamide must have been discontinued at least four weeks before the baseline PSA evaluation (before the start of chemotherapy), whereas bicalutamide must have been discontinued at least six weeks beforehand, as to avoid the possibility of confounding results due to the response to anti-androgen withdrawal.

Patients who received docetaxel plus prednisolone were treated as follows: docetaxel (75 mg/m^2) administered intravenously over one h period on day one, every three weeks. Prednisolone (5 mg, bid) began on day 1 and continued throughout the treatment. Prior to chemotherapy, patients were premedicated with dexamethasone (20 mg i.v.) at 12 and 6 h prior to chemotherapy followed by diphenhydramine (50 mg, i.v.) and cimetidine (300 mg, i.v.) 30 min prior to therapy to prevent the onset of hypersensitivity reactions and reduce and/or delay skin toxicity and fluid retention. Patients received the antiemetic granisetron (3 mg) or ondansetron (8 mg) i.v. just before chemotherapy.

Chemotherapy administration continued until disease progression or unacceptable adverse effects. Patients underwent restaging after four cycles of chemotherapy. If PSA increased after starting treatment, chemotherapy continued for at least three cycles because of the possibility of a PSA surge. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (CTC) version 3.0.[8]

Statistical analysis

PSA response was defined as a reduction of at least 50% in the baseline levels as confirmed by a second PSA test three weeks later. In non-responders, PSA progression was defined as a 25% increase over the nadir value, as confirmed by a second value. In patients who experienced progression after the initial PSA response, PSA progression was defined as a 50% increase over the nadir value confirmed by a second PSA value. In all patients, progressive disease was determined according to RECIST criteria, development of new lesions as visualized on a bone scan, or two consecutive PSA increases separated by ≥3 weeks over the PSA nadir that was achieved by androgen

Table 1. Patient characteristics (n=37).

Characteristics	Number of patients
Age, median (years)	66 (range: 60-70)
PSA median (ng/ml)	79 (range: 16-1100)
Hb, mean±SE (g/dl)	10.9±0.3
ECOG performance status	
<2	23 (62%)
2	14 (38%)
Pain at presentation	28 (76%)
Site of metastasis	
Bone	26 (70%)
Lymph node	10 (27%)
Liver	2 (5%)
Lung	5 (14%)
Initial treatment	
Surgery	6 (16%)
Radiotherapy	19 (51%)
Hormonal therapy	12 (32%)
Gleason score	
≤8	8 (22%)
>8	29 (78%)
Analgesics	28 (76%)
Zoledronic acid	18 (49%)

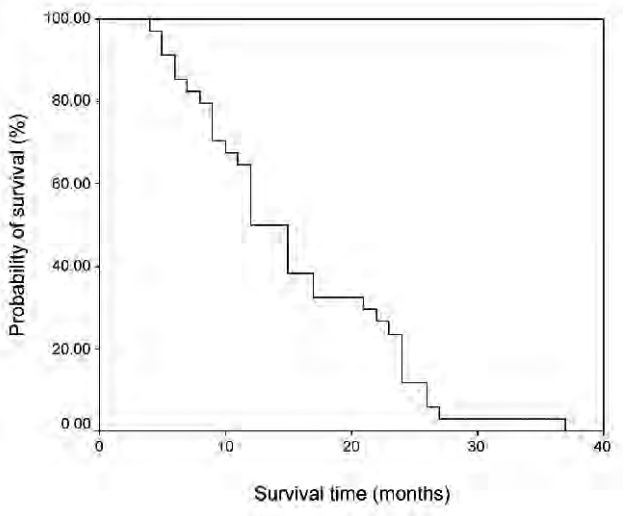

Figure 2. Overall-survival in months (n=34).

Table 2. Initial PSA response (n=34).

	Response			
	Complete n(%)	**Partial n(%)**	**Stable n(%)**	**Progression n(%)**
PSA	3 (8.9)	11(32)	17(50)	3 (8.9)

deprivation therapy. Pain response was defined as a reduction in the requirement of analgesic drugs.

The Kaplan-Meier estimate was used for survival analysis. Event-free survival was determined to be the time interval between the date of chemotherapy initiation and either PSA progression or progression of measurable tumor. Overall survival was defined as the time interval between initiation of chemotherapy and the date of death or last follow up. Following univariate analysis, we performed multivariate Cox regression analysis to elucidate the combination of the variables that could be used to predict survival. $P<0.05$ were considered statistically significant. Analyses were performed using SPSS version 10.

Results

Patient characteristics

Table 1 shows the characteristics of the 37 patients. Patients' median age was 66 (range: 60-70) years and the median serum PSA level was 79 (range: 16-1100) ng/ml. All patients received hormonal therapy with luteinizing hormone-releasing hormone agonist (LHRHa) and antiandrogens. Most (70%) had bone metastases. Analgesics were given to 28 (76%) patients, while zoledronic acid was administered to 18 (49%) at the initiation of chemotherapy. Prednisolone was given to one patient as a single agent, whereas two patients received vinorelbine as a single agent. The majority of patients (34) received docetaxel plus prednisolone.

Response, survival and toxicity for docetaxel plus prednisolone

The median number of cycles was six (range: 4-11). Of the 34 patients who received docetaxel plus prednisolone, 14 (41%) achieved at least a 50% decrease in serum PSA levels. Among the 16 patients who had measurable disease at baseline, 8 (50%) achieved a partial response according to radiographic criteria. Among the 25 patients who had cancer pain before treatment initiation, 15 (60%) reduced their analgesic drug intake (Tables 2-4).

The most common grade 3-4 toxicity attributed to chemotherapy was neutropenia. Grades 3-4 neutropenia occurred in 13 out of 34 (38%) patients while febrile neutropenia was reported in 2 (6%). Growth factors were used to manage neutropenia. As seen in Table 5, the most frequent non-hematologic grade 3-4 adverse events were sensory neuropathy in 4 (12%) patients and general fatigue in 5 (15%). No second-line chemotherapy was given for progression.

The median follow-up period was 13 months. Kaplan-Meier estimate for event-free and overall survival is shown in Figures 1 and 2. The median event-free survival was 7 (range: 4-31) months and the median overall survival was 12 (range: 4.5-37) months. According to univariate analysis the following pretreatment parameters were noted to be significant prognostic factors that affected survival: prechemotherapy hemoglobin level ($P=0.0001$), prechemotherapy PSA level ($P=0.0001$), multiplicity of metastatic sites ($P=0.001$), pain ($P=0.018$), performance status ($P=0.00$), and time to hormone independence ($P=0.00$). Multiplicity of metastatic sites was the sole independent prognostic factor ($P=0.005$) according to multivariate analysis (Table 6).

Discussion

The process by which HRPC cells are generated appears to be varied. Cytokines such as IL-6 have been shown to initiate an alternative signaling pathway, in comparison to the androgen receptor signaling pathway. IL-6 induces growth of neuroendocrine cells or neuroendocrine-like features in cells in HRPC. The increased presence of neuroendocrine cells in HRPC signifies a

Table 3. Initial response at 16 different measurable metastatic sites.

Site of metastasis	Response			
	Complete n(%)	Partial n(%)	Stable n(%)	Progression n(%)
Bones	0 (0)	4 (25)	0 (0)	0 (0)
Lymph nodes	0 (0)	3 (19)	7 (43)	0 (0)
Liver	0 (0)	0 (0)	0 (0)	1 (6)
Lungs	0 (0)	1 (6)	0 (0)	0 (0)

change in the prostate cell microenvironment. The stromal microenvironment also influences the development of HRPC. In addition, intracrine androgen metabolic enzymes play a significant role in the development of the hormone refractory process. The androgen receptor has been characterized and shown to differ in sequence in HRPC compared with androgen-sensitive prostate cancer cells. These variants of the androgen receptor through sequence changes may preserve the basic function of the molecule, but have far-reaching consequences on the cell as a whole.[9]

The criteria of the Egyptian patients enrolled in this study were to some extent similar to those of other patients with prostate cancer according to the literature, who had a median age of 66 years and the majority presented with bone and lymph node involvement. Notably, however, 78% of patients in this study had tumors with a Gleason score of more than 8. This was slightly higher than the Gleason scores observed in patients in the TAX 327 study.

Regarding the efficacy of docetaxel in combination with steroids for the treatment of HRPC, basic research has shown that steroids enhance the cytotoxicity of docetaxel against HRPC in both in vitro and in vivo experiments. Furthermore, it has been suggested that the mechanism of this combined treatment for HRPC might be associated with potentiation of the anti-angiogenic activity of docetaxel by steroids.[10]

In the TAX 327 phase III randomized trial,[6] the weekly docetaxel-based regimen was less toxic than the three-weekly regimen. However, the three-weekly regimen demonstrated a survival advantage (18.9 vs. 16.5 months, P=0.009) in addition to improved response rates in terms of pain, serum PSA levels where the PSA response reached 45%, and QoL which led to approval by the USA FDA in 2004 and by the European EMEA in 2005. Similar to various literatures, in the present study the PSA response rate did not reach 50%,[6, 11, 12] and the median overall survival time was only12 months. This low survival figure might have been the result of ethnic differences, poorer socioeconomic standards, a larger number of patients with extensive metastases or those with high Gleason score tumors. Of note, ethnicity plays a role in prostate cancer. White et al. have observed ethnic disparities in survival among males diagnosed with prostate cancer in Texas in a study of 87449 patients. After adjusting for socioeconomic status, age, tumor grade and stage, they noted that Hispanic and black males were more likely to die from prostate cancer than white males.[13]

The present study has found only one independent prognostic factor which might be secondary to the limited number of patients. However larger studies are helpful in understanding the different prognostic factors for metastatic prostate cancer. Wyatt et al. have researched variables that affected survival among 379 men treated for HRPC. Independent prognostic factors included age, serum hemoglobin level, time to hormone-independent disease,

Table 4. Initial pain response (n=25).

	Response			
	Complete n(%)	Partial n(%)	Stable n(%)	Progression n(%)
Pain	0 (0)	15 (60)	7 (28)	3 (12)

Table 5. Grade 3 and 4 toxicities (n=34).

Parameter	Grade 3		Grade 4	
	n	%	n	%
Hematologic:				
Neutropenia	12	35	1	3
Thrombocytopenia	3	9	-	-
Anemia	3	9	-	-
Non-hematologic:				
Neurosensory toxicity	4	12	-	
Nausea and vomiting	1	3	-	
Fatigue	4	12	1	3
Toxic hepatitis	1	3		

treatment group and the extent of metastasis.[14] Armstrong et al. have identified independent prognostic factors which impacted survival through an analysis of the TAX327 study of 1006 patients. Those factors included the presence of liver metastases, number of metastatic sites, clinically significant pain, Karnofsky Performance Status, pretreatment PSA doubling time, tumor grade, alkaline phosphatase and hemoglobin levels.[15] These prognostic factors can affect the timing of interference with chemotherapy.

Interstitial pneumonitis has sporadically been reported as a toxic effect of taxanes.[16] In the present study no interstitial pneumonia was observed. It has been reported that a high cumulative dose of docetaxel and past history of lung disease were risk factors for severe interstitial pneumonia.[17,18] Thus, it would be advisable to consult a lung specialist when pneumonitis is even remotely suspected.

According to different studies, there is variability in the incidence of severe hematologic toxicity. In the TAX327 study, the incidence of grade 3-4 neutropenia in the triweekly arm was 32%, with 3% febrile neutropenia.[6] In the present study we observed grades 3-4 neutropenia in 38% of the patients and febrile neutropenia in 6%. However an Italian study reported only a 12.5% incidence of severe neutropenia.[19] In contrast, Japanese studies have reported values of severe neutropenia of 93% and 85%.[11,12] Could these variances be attributed to ethnic differences? However, these adverse events could be controlled to a great extent by the administration of granulocyte-colony stimulating factor.

In the current study, retrospective analysis of patients' records revealed that the use of estramustine plus docetaxel was not a preferable treatment policy, primarily due to toxicity. In the SWOG 99-16 trial,[20] patients were divided into two groups, docetaxel (60 mg/m^2 every 3 weeks combined with estramustine (280 mg orally, tid on days 1-5) vs. mitoxantrone (12 mg/m^2) combined with prednisone (10 mg qd). Median overall survival with docetaxel and estramustine (17.5 months) was significantly longer than with mitoxantrone and prednisone (15.6 months, P=0.02). Patients who received docetaxel and estramustine had significantly higher rates of grade 3 or 4 cardiovascular events (15%) compared to those who received mitoxantrone and prednisone (7%, P=0.001). The incidence of these additional toxicities was reduced at a lower estramustine dose and the provision of anticoagulant prophylaxis.[21] However the attitude towards estramustine did not change by the institutions involved in the present study.

Drouin et al. discussed the issue of starting chemotherapy in advanced prostate cancer prior to hormone independence. They concluded that even minimal chemotherapy side effects should be taken into consideration for any therapeutic decision.[22]

Few reports[23,24] concerning the reinduction of hormone-sensitivity in HRPC patients following chemotherapy have been published. This issue has not been evaluated in large studies and was not addressed in the patients' records in the present study.

Table 6. Cox multivariate analysis (n=34).

Variables in the Equation					
				95%CI for Exp(B)	
	B	*p*-value	Exp B	Lower	Upper
Hemoglobin	-1.854	0.052	00.157	0.024	001.015
PSA	0.687	0.504	01.988	0.265	014.893
No. of metastatic sites	4.038	0.005	56.721	3.359	957.703
Pain	0.511	0.409	01.668	0.496	005.612
ECOG	0.557	0.565	01.745	0.262	011.611
Time to hormone independence	1.413	0.124	04.108	0.680	024.806

New agents are being extensively studied for HRPC and include such antiangiogenic agents as bevacizumab; multitargeted tyrosine kinase inhibitors (TKIs) such as sorafenib and vatalanib that inhibit angiogenic growth factor receptors (VEGF); mTOR inhibitors; atrasentan (a highly selective endothelin A receptor antagonist); and calcitriol.[25-27] Future trials will determine the extent to which these agents change the outcome of HRPC.

With effective chemotherapy for HRPC, the need for focused palliative care cannot be overemphasized. Lower urinary tract, skeletal, and hematological problems, lymphoedema, rectal infiltration, pelvic pain, neurological problems, and psychological dysfunction are all problems known to impair QoL. It is of utmost importance to define the basic clinical problem and provide the appropriate care in a judicious manner.

Conclusion

HRPC is not considered totally resistant to chemotherapy. In this study, multiplicity of metastatic sites is the only independent prognostic factor. Thus, further research is necessary in order to attain a better treatment outcome.

Conflict of interest statement:

No conflict of interest exists.

Acknowledgements

The author expresses his appreciation to the employees in the Archives at the Clinical Oncology and Nuclear Medicine Department of Mansoura University for their cooperation.

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