

Role of Estrogens in the Secondary Hormonal Manipulation of Hormone Refractory Prostate Cancer

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Introduction

Hormone refractory prostate cancer is a leading cause of cancer related death in males in the western world. In 2003 alone, it was estimated that 28,900 deaths would occur due to carcinoma prostate in the United States.¹ Due to lack of mass screening programs, the incidence of prostate cancer is perceived to be much less in the developing world and hence, only a minority of patients are found to have localized disease.^{2,3} As majority of patients in the less developed countries seek medical attention with symptoms and complication of advanced prostate cancer, early development of hormone refractory status is observed and a short course towards the terminal event in metastatic hormone refractory cancers is seen.⁴

The role of hormonal manipulation in prostate cancer was first established in the mid twentieth century when Huggins and Hodges demonstrated that castration and administration of estrogens resulted in regression of disease, which was reversed by administration of testosterone.⁵ However this regression is not durable. Majority of patients initially treated with androgen blockade would exhibit regression of disease however the median duration of response is brief.⁶ At this point in the natural history a proportion of patients may still be sensitive to secondary hormonal manipulation and chemotherapy.^{7,8} These interventions result in improvement in survival and quality of life for some patients.⁹ A gold standard in treatment of HRCP is yet to be set, various protocols have been developed in the past, including the use of different derivatives of estrogens e.g fosfestrol (diethylstilbestrol disphosphate, Honvan, Asta pharmaceutical TM) for treating HRCP. Direct cytotoxic effect of this therapy was proved in trials with continuous infusion of high dose of fosfestrol.^{10,11} This effect

has resulted in more than 50% regression of biochemical disease with a majority of patients experiencing marked subjective improvement in symptoms.¹²

As a significant proportion of patients present with advanced cancer and develop hormone refractory prostate cancer, there is a need to define a protocol which would lead to regression of disease, increase survival and reduce or delay suffering. The role of Fosfestrol (Honvan) in the control of disease in hormone refractory prostate cancer was reviewed.

Patients and Methods

All the patients diagnosed as hormone refractory prostate cancer and treated with Fosfestrol (Honvan) from January 1991 to December 2001 were included. Hormone refractory prostate cancer (HRPC) was defined as a state when despite androgen blockade by either surgical or medical castration there is progression of disease manifested by either a rise in prostate specific antigen (PSA) or development of new metastasis on imaging studies. Twelve patients received 500mg of Injection Fosfestrol (Honvan) intravenous diluted in 100cc of normal saline and infused over 2-3 hours on the first day followed by 1000mg for the five days. There after they received a maintenance oral dose of 120 mg thrice daily. During hospitalization they were given deep vein thrombosis (DVT) prophylaxis with 5000 IU of heparin subcutaneous twice daily and on discharge they were prescribed, 1 mg of warfarin and 300mg of aspirin once daily. During the therapy they were regularly monitored for development of DVT, cerebro-vascular accident (CVA), congestive cardiac failure, gynaecomastia and other complications.

The stage at presentation, primary mode of treatment, mode of androgen ablation, nadir PSA, period of remission, PSA before fosfestrol treatment,

PSA doubling time before and after the treatment, duration of response, and overall survival were recorded. A drop in PSA of >50% was classified as major response. The drop of <50% was defined as minor responders. Non-responder was defined as a rise in PSA > the level prior to the start of treatment after excluding other causes of raised PSA. The disease progression on imaging study was also recorded as treatment failure. The duration of response was defined as the period from the start of treatment to progression of disease on imaging studies or a PSA level, double the pre-treatment level. The overall survival was recorded. The morbidities and mortalities related to treatment were also recorded

Results

During the 10 year period, 12 patients with HRPC were treated with estrogens (fosfestrol) according to the defined protocol. The mean age at presentation was 66.6 + 5.4 years (range 57-73). Seven patients (58%) reported lower urinary tract symptoms, two patients (17%) each presented with urinary retention and pathological fracture and one patient (8%) had bowel obstruction. At the time of initial diagnosis, 3 patients (25%) had localized disease and underwent definitive external beam radiation therapy and nine patients (75%) had metastatic disease (stage D-2). Six patients (50%) underwent Channel TURP. Six patients each opted for orchidectomy or medical castration (LHRH analogs). Two patients received palliative radiation to metastatic lesions. Two patients also received fosfestrol initially along with other forms of treatment because of high volume of biochemical and bone disease. One patient had well differentiated tumor, six had moderately differentiated tumor and five had poorly differentiated tumor. The mean initial PSA was 340 + 728.1ng/ml (range 4.1-2375, Median 94). Three patients who presented in acute retention of urine did not have a PSA before androgen ablation. The overall mean period of remission was 25.3 + 24 months, however mean period of remission for advanced disease was 16+18 months. Six (50%) patients had major response and 4 (33%) had minor response. Two (17%) patients had no response. The mean PSA before receiving Fosfestrol was 60.5 + 82 ng/ml (range 0.013-246). The PSA after treatment was 24.3 + 33.2 ng/ml (range 0.9-81.3). Although there was a decline in the PSA it was not statistically significant (p-value 0.24). One patient with very high PSA of 2375 was excluded. The PSA doubling time before the treatment was 2.7+1.7 months and increased to

3.9+2.4 months after the treatment. Although a difference was observed it was also not statistically significant. The mean duration of response was 12.7 + 14.3 months (range 1-38 months). The mean follow up was 13.6 + 12 months (range 1-38 months). Two patients died of non cancer related causes. One patient had aggressive disease; he did not respond to fosfestrol and died of cancer related causes. One patient died of cancer, nineteen months after receiving Fosfestrol. There was morbidity each of gynaecomastia and congestive cardiac failure.

Discussion

The transformation of prostate cancer from an early hormone sensitive status to progressive, metastatic hormone refractory cancer has been the focus of prostate cancer research in the last decade. The molecular basis for this phenomenon is not well elucidated. No single agent or combination can yet claim to fulfill the long-term goal of achieving cure. The current goals are more modest i.e. to identify agents that would increase survival, cause regression of disease and most important of all improve the quality of life. In our part of the world where the disease presents at an advanced stage the need to identify a protocol that is also cost effective is crucial. We attempted to achieve this lesser goal with the use of Fosfestrol (C18 H18 Na4 CO8 P2). It is a synthetic non-steroidal phosphorylated estrogen and requires dephosphorylation to diethylstilbestrol before its activation. It is readily absorbed orally. The intra venous and orally administered drug is metabolized in the liver; a portion is excreted in the bile but is reabsorbed through the entero-hepatic circulation and the conjugates are excreted in the urine. In the past Droz et al have demonstrated that this form of estrogen can be safely used to circumvent the hormone resistance and produce tumoricidal effect.¹⁰ He recommended a dose of 4gm/day over 3.5 hours and reported side effects mainly as nausea, vomiting and fluid retention. As majority of the men suffering from HRPC also have concurrent medical problems. The goal of palliation is to produce disease regression with minimal side effects. To achieve this objective we attempted to reproduce the tumoricidal effects using lesser dosages. During the six-day infusion minimal nausea was reported and all the patients were able to tolerate three full meals per day. During the maintenance period none of the patients reported nausea. No patient developed any significant cardiovascular or thrombo-embolic side effect. This demonstrated the excellent tolerability of lesser doses (1 gm/day).

An important consideration in the management of cancers in the developing world is the cost of treatment. Most chemotherapeutic agents are expensive. The cost of this drug at our institute was Rs 1190 (USD\$ 20) for the intravenous use and Rs. 45/day (USD\$ 0.70) for maintenance therapy which is one of the least expensive forms of treatment currently available.

Kelly et al demonstrated that a >50% decline in the PSA level is predictive of improved survival.¹³ Six out of twelve of our patients demonstrated a >50% decline and 4 patients showed a <50% decline in the PSA. This 83% response is far more than response rate of 29% reported with Mitoxantrone and Prednisone.⁹ Even more toxic agents like Doxorubicin and Estramustine have reported a response rate of 54%.⁸ The mean duration of response 12.7 + 14.3 months is comparable with the response duration of 10.75 months with Mitoxantrone and Prednisone combination.⁹

In conclusion synthetic estrogens are well tolerated and relatively inexpensive agents. The described protocol of administration of fosfestrol can be considered for palliative use against hormone resistant prostate cancer.

References

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Abstract

Objective: To evaluate the role of Estrogens (Honvan) in the secondary hormonal manipulation of patients with hormone refractory prostate cancer (HRCP).

Methods: Twelve patients diagnosed as hormone refractory prostate cancer received intravenous estrogens for six days (Fosfestrol, a synthetic phosphorylated estrogen derivative), followed by a maintenance oral dose of 120 mg thrice daily as second line hormonal treatment. During the treatment they were given deep venous thrombosis prophylaxis. Their stage at initial presentation, primary treatment, mode of androgen ablation, prostate specific antigen (PSA) level, duration of remission prior of HRPC status, PSA doubling time before and after estrogen treatment were recorded. The morbidity and mortality of the treatment was also recorded. A drop in PSA of > 50% was classified as major responder. The drop of < 50% was defined as minor responders. Treatment failure was defined as a rise in PSA > the level prior to the start of treatment.

Results: The mean age at diagnosis of prostate cancer was 66.6 + 5.4 years (range 57-73). At the time of initial diagnosis only 3 patients (25%) had localized disease and 9 (75%) had metastatic prostate cancer. Six patients each opted for surgical or medical castration (LHRH analogs) as the mode of androgen ablation. The mean initial PSA at diagnosis was 340 + 728.1 ng/ml (range 4.1-2375, Median 94). After development of HRPC, six patients (50%) had major response, four (33%) had

minor response to estrogen administration. Two patients (17%) did not respond to estrogens. The mean PSA before receiving Fosfestrol was 60.5 + 82 ng/ml (range 0.013-246). The PSA (nadir) after treatment was 24.3 + 33.2 ng/ml (range 0.9-81.3). One patient developed gynaecomastia and one had congestive cardiac failure. Two patients died of non cancer related deaths and one patient died of cancer related death.

Conclusion: Synthetic estrogens are well tolerated, in-expensive agents and could be considered for palliative use against hormone resistant prostate cancer (JPMA 54:445;2004).