Metastatic Prostate Cancer

I. Mehdi (Pakistan Medical Research Council, Research Centre, Jinnab Postgraduate Medical Center, Kar

Prostate Cancer is the second commonest male malignant tumor. It is the most commonly diagnosed nondermatological tumor in males beyond the age of 50 years[1-3]. It is the second leading cause of cancer related mortality in men (35000/year in Europe)[4]. It is a major concern of morbidity and cost in health care in aging male population in developed world. The lifetime risk of developing a microscopic, clinical disease and prostate cancer related death are 30%, 10% and 3% respectively[5]. About 85% of diagnosed cases have skeletal metastasis at presentation or will develop it in due course of disease. In local population the frequency of Cancer Prostate (CAP) is 3.1% while the incidence is 5.4/100000/ year[6].

The epithelial cell clones in CAP are of three distinct variety; testosterone dependent, testosterone sensitive, or testosterone independent[7]. It is the relative ratio of these cell clones in a given CAP, which determines its biologic behavior, sensitivity to hormonal manipulation and predicts treatment response. Androgens in male come from testes (80-85%) and adrenals (15-20%). Testosterone deprivation can cause mediated tumor cell death by apoptosis and an objective response of 30-40% can be observed in a virgin disease indicated by normalization of PSA (<4 ng/ml) in upto 80% of cases within 3-8 months time[7]. A fall in PSA >80% of its initial baseline value within 4 weeks, is always taken as a good prognostic indicator. A clonal selection of androgen (testosterone) independent cells is inevitable and usual time to this 'escape phenomenon' is 18-30 months on the average[8].

Normal PSA value for an individual is dependent on his age and volume of his prostate gland[9]. A higher PSA is seen after prostate massage (twice the normal) and cystoscopy (four times higher), but it returns to baseline within 2-6 weeks time. A PSA velocity of more than 0.75 ng/rnl/year is suggestive of a malignant prostate disease. PSA density (PSA/Prostate volume) and a ratio of free and bound PSA are more reliable indicators of malignancy than a simple PSA value[9]. A PSA >50 ng/ml mandates a prostate biopsy. Testosterone levels of an adult male are 2-8.1 ng/ml, while at castration they should reach less than 1.0 ng/ml.

The treatment options in advanced CAP are endocrine manipulation, radiation therapy, biphosphonates and systemic chemotherapy[10,11]. The endocrine manipulation is aimed at depriving the tumor from testosterone influence either by sub-capsular orchiectomy (surgical), or by androgen blocking drugs (medical). The drugs used can be steroidal (suicidal) or non-steroidal antiandrogens {cyproterone acetate, flutamide, biclutamide, nilutamide), LHRH analogues (goserline, buserelin, leuprolide) and estrogens. A few drugs like ketoconazole, estramustine and suramin[12,13] have also a therapeutic influence on CAP by yet exactly undetermined/unexplained mode of action. The intermittent androgen suppression (lAS) compared to continuous suppressive therapy is superior in terms of better Q0L (quality of life), low cost of treatment and a low toxicity profile[14]. Surgical androgen blockade has the advantage of better patient compliance, lower cost; and is superior in cord compression, renal failure or ureteric obstruction[15]. Radiation

therapy can be used either by teletherapy (So called spot-welding of symptomatic skeletal metastasis), brachytherapy, or systemic strontium (isotope labeled elements)[16].
Biphosphonates are a group of compounds used orally or by intravenous route to cause bone stabilization, improve skeletal pains and to prevent skeletal related events (fractures or compression). The used biphosphonates are etidronate, clodronate, pamidronate, or alendronate, Systemic chemotherapy is in its initial experimental stages and is yet to find a substantial place in management of CAP[17]. The active chemotherapeutic agents are taxenes, estramustine phosphate, cyclophosphamide, 5-fluorouracil, dacarbazine and cisplatin[18].
He side effects of hormonal therapy are psychological non-acceptance (24%), initial flare/aggravation of symptoms (29%), sweat, hot flushes, surgery related hematoma or infection (10%), gynaecomazia, erectile dysfunction, nausea, vomiting, asthenia, hepatic dysfunction, bone loss and muscle wasting[19]. The causes of inappropriate, erratic, or suboptimal response are androgen receptor abnormalities, ratio of hormone dependent/sensitive clones, defect in activation of apoptosis, ectopic androgen secretion, adrenal hyperplasia or tumor, quality/efficacy of anti-androgen medicine, pancreatic tumor or drug interactions[20].
The cost versus efficacy is an important consideration of any treatment in the developing world. Surgical testosterone ablation is superior to LHRH analogues in terms of cost, compliance and time to progression. SCOT is underutilized in CAP management. It is a rapid, efficient, compliant and durable mode of hormonal therapy. A higher PSA is directly related to skeletal metastasis.
The new approaches in metastatic CAP treatment are newer effective molecules for androgen suppression, gene therapy (correction/repair of defective genes), application of suicide genes in a pro-drug system, transcription/transduction targeting, vaccines for CAP, immune-therapy (activated Tlymphocytes), cell differentiation, agents, inhibition of signal transduction, inhibition of cell-cell interaction, anti-sense compounds, matrix metalloproteinases and antiangiogensis molecules[18]. The eligible patients for these experimental approaches are those with an increase in size of measurable disease, increase in sites of disease, appearance of new skeletal lesions, a persistently elevated PSA (>5 ng/mt) in a biopsy proven CAP with no measurable disease, two consecutive rises in PSA at least I week apart, progression after anti-androgen withdrawal and evidence of gonadal suppression in the castrate range[18].

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