Hormone refractory metastatic prostate cancer

Prognostic factors

Hormone-refractory prostate cancer is defined as progressive disease despite castration serum levels of testosterone. No effective systemic treatment has been clearly established for this condition. In patients with prostate cancer predictive factors such as stage, grade, size and extent of the primary tumor, and the presence or absence of distant metastases, have been established. Factors such as age, degree of pain, performence status, associated chronic disease, and a series of biologic parameters are less widely accepted [1].

In this issue of *Annals of Oncology*, Fosså et al. present a retrospective study of symptomatic patients with painful metastases, primarily referred for radiotherapy [2]. The authors have created a prognostic model based on four independent clinical variables: performance status, creatinine, alkaline phosphatase, and duration of response to hormone treatment ≤1 year. Prostatic acid phosphatase was not a significant variable, but the value was missing in 17%, and prostate specific antigen (PSA) was not analysed. Following androgen deprivation, the pretreatment serum testosterone level and the number of bone metastases on bone scan have been reported as important variables in other studies [3, 4].

The present study differs from other prospective clinical trials of prognostic factors which often select good risk patients. The EORTC analyzed 436 previously untreated patients, and found performance status was the most important prognostic factor followed by acid phosphatase for stage M0 patients and alkaline phosphatase, T category, and the presence of associated chronic disease for M1 patients [1]. A Canadian study found that only serum testosterone and extent of disease on bone scan influenced survival [5]. The observation that patients with low pretreatment testosterone levels were less responsive to androgen deprivation has been made by various investigators [6]. Perhaps this condition selects growth of cells which are less androgen dependent.

While changes in PSA are a good indicator of disease activity in men with metastatic prostate cancer treated with hormonal manipulation, the role in patients treated with second line therapy is less clear [7]. A trend towards decreased survival has been observed with increasing values of PSA [5]. However, correlations between response in measurable disease and biochemical response of serum acid phosphatase and PSA suggest that treatment decisions shouldn't be based on these parameters alone [8].

Other new potential prognostic factors include Ki-67 monoclonal antibody which may provide additional information to traditional histopathological grading criteria [9].

Hormonal therapy

Treatment of advanced prostate cancer centers around hormonal manipulation. Monotherapy with orchiectomy, estrogens, or lutenizing hormone-releasing agonists produce successful palliation in up to 80% of patients. With standard monotherapy 50% will live less than 2 years, and 90% will die within 3 years [17].

The value of total androgen blockade remains controversial. Different studies have contradictory results. It is difficult to appreciate whether this may be due to variations in the therapy, different end points or differences in patient selection and therefore in prognostic factors [11, 12]. Crawford has reported that androgen blockade with leuprolide and flutamide results in a longer progression-free survival and over-all survival than with leuprolide alone, and the subset with minimal disease and good performance status appear to benefit the most [12]. Similarly a Canadian study demonstrated benefit from total androgen blockade [13]. Here, stratification according to prognostic factors was not done. The EORTC evaluated bilateral orchiectomy versus zoladex and flutamide. Time to progression was delayed with medical treatment compared with orchiectomy, but no difference in survival was detected [11].

With prostate cancer contrary to breast cancer, the development of hormonal resistance is an irreversible event which predictably occurs after androgen deprivation. The median time to progression is from 12–18 months. Response to second line therapy is rare, and does not impact upon survival. The median survival after progression is approximately 6 months [14]. Bone is the primary and only site of metastases in 65% of patients who present with metastatic prostatic cancer. Objective measurable or evaluable criteria for response evaluation are often lacking. And there is a tendency to try to use other criteria for evaluation such as performance status, acid phosphatase, PSA, analgesic requirement and prostate size [14]. Subjective criteria must also be considered. In many patients bone pain and decreased performance status are predominant, and relief of these symptoms is as important as prolongation of survival.

Second-line hormonal therapy

Management of the hormone-refractory patient is an exceedingly difficult problem. In patients whose serum testosterone remains at anorchid levels, there is little evidence to suggest that changing the form of androgen deprivation will achieve disease control. Yet patients are not always completely hormone resistant. The rationale for secondary hormonal treatment is based on the idea that suppression of circulating adrenal androgens may cause further tumor regression by suppressing any remaining hormone dependent prostatic cancer cells. Symptom relief often occurs rapidly, suggesting a mechanism other than adrenal suppression.

Secondary hormonal therapy, first attempted by Huggins in 1945 with bilateral adrenalectomy, may be accomplished in a variety of ways [15]. Surgical adrenalectomy or pituitary ablation are not used today. Drugs which achieve a medical adrenalectomy include aminoglutethimide, and ketoconazole. Aminoglutethimide, a potent inhibitor of adrenal steroidogenesis, in association with hydrocortisone may be effective in reducing serum testosterone and dihydrotestosterone. Partial response (PR) is seen in 17%–21% of patients, with subjective improvement in up to 60%. Significantly prolonged survivals, though uncommon, have been reported in responders. It is difficult to determine whether or not the required cortisone is responsible for the beneficiary effects. Erythematous rash and lethargy are the most commonly reported side effects [15, 16].

Flutamide may or may not be effective as second-line hormonal therapy. Labrie reports a response rate of 35%, including stable patients. The median life expectancy of responders was 2.5 years; 8 months for nonresponders [17]. Sogani treated 26 patients who failed orchiectomy or DES. Response was achieved in 23%. The duration of response was 3 to 22 months [18]. Fossâ found subjective response in 5/25 (20%) hormone-refractory evaluable patients [19].

Megace, megesterol acetate, or dexamethasone are less expensive secondary hormonal therapies. Objective responses are low, however in the order of 10%. Usually, the best response is stable disease, with median survival of less than 1 year following progression [20].

Chemotherapy

Hormone-resistant adenocarcinoma of the prostate is refractory for the most part to second-line hormonal therapy. It must also be considered a chemotherapeutically resistant tumor despite the wide disparity in reports suggesting efficacy of 40% to 80%. Objective tumor regression occurs in less than 10% to 20%. Most responses are only partial and have minimal impact on survival in randomized phase III trials. Eisenberger reviewed overall objective responses in 3184 patients. The CR and PR rate was 7% (202 patients), and when the category of STAB was added (CR+ PR+ STAB) this increased only 15% to 22% (485 patients) [21].

Some agents may possess marginal to modest antitumor activity, but the unique proponderance of osseous metastases as the major parameter to measure response has hampered clinical trials. The variable natural history, the absence of accurate, reliable biochemical and biological tumor markers or of bidimensionally measurable lesions have necessitated the use of changes in subjective parameters (quality of life scales, weight, analgesic use, performance status, sense of well-being), as well as changes in serum or prostatic acid and alkaline phosphatase, and anemia as response criteria. Conclusions of many earlier trials are hindered by the use of evaluable lesions such as bone scans, IVP, digital rectal exams, and peripheral edema. If trials are limited to only patients with bidimensionally measurable parameters, no more than 10%–20% of patients with advanced prostate cancer are eligible [8, 14, 22].

A variety of single agents have undergone clinical trials. Many oncologists in the United States use weekly adriamycin as first-line therapy in hormone-resistant cases. At Memorial Sloan-Kettering Cancer Center (MSKCC), only 5% of 39 patients (95% confidence limits 0–12%) responded. With weekly 20 mg/m^2, 12% of 32 cases had a PR [23]. The Northern California Oncology Group using National Prostate Cancer Project (NPCP) criteria (CR+ PR+ STAB) observed remission in 53%. In 25 patients having a median KPS of 70, and all having been previously treated with hormones and 84% with radiation therapy, 84% had a response by NPCP criteria, while 4/12 (33%) with bidimensionally measurable lesions responded [24].

Other chemotherapeutic agents in the literature which have demonstrated some activity include cyclophosphamide fluorouracil, methotrexate, mitomycin C (by the EORTC), vinblastine, and vindesine, studied with a wide variety of response criteria [25, 26]. Vinblastine was recently re-evaluated using a novel pharmacokinetic schedule. The vinca alkaloid given at 1.5 mg/m^2/d for 5 days every 4 weeks, seems more active than when given weekly. The response rate was 21% in 39 cases. Although the median response duration was only 28 weeks, toxicity was notable and the efficacy of this schedule requires confirmation [25].

Other interesting single agents include gallium nitrate which inhibits bone absorption and produces hypocalcemia. When administered by continuous infusion ×5 days to 23 patients, remissions were seen in 10%, but of short duration [27]. Polyamine conversion, increased in normal prostate glands and in prostatic cancer, can be inhibited by mitoguazone. In a highly selected patient population with soft tissue lesions such as lung and nodes, 24% of 25 patients had a PR. There was no effect on osseous lesions [28]. In another trial employing a similar dosage schedule, mitoguazone was inactive in 19 patients [29]. Trimetrexate, a new antifol,

was evaluated at MSKCC in 31 men with soft tissue lesions. Only 5 (17%) achieved PR. The median duration of response was only 3 months [8].

The FAM combination (5-fluorouracil, adriamycin, mitomycin) is best known for its use in gastric and pancreas tumors. Based upon the reported 35% response rate at the M.D. Anderson Hospital in prostate cancer, a Southwest Oncology Group trial was initiated. The overall response rate was 16% in 68 adequately treated patients [30].The EORTC obtained a 28% response with mitomycin alone. Combining 3 marginally active drugs probably doesn't produce better results, particularly in this elderly patient population. Another combination which needs verification is the report of cisplatin and continuous infusion fluorouracil combination. Three PR in 7 patients with bidimensionally measurable disease was reported. Eight of 23 had a >50% decrease in acid phosphatase, and 12/24 had a >50% decrease in PSA [31].

A randomized trial of combined versus sequential chemo-endocrine therapy evaluated the results of chemotherapy given earlier in the course of disease. Patients were randomized to receive chemotherapy (adriamycin and cyclophosphamide) either at the time of hormonal therapy or at the time of progression. The combination arm had a higher response rate than the sequential arm (63% versus 48%), but no significant differences in survival [32].

Androgen priming to increase the sensitivity of prostate cancer chemotherapy has been attempted. When only evaluable patients were considered, the stimulation arm had a higher response rate (85% versus 72%), but more patients were inevaluable (41% versus 16%), as a result of the unacceptable toxicity associated with androgen stimulation. No significant differences in survival have been found [33].

Estramustine (estracyt), the combination of nornitrogen mustard and estradiol has shown activity in experimental systems refractory to estrogen, and been extensively studied in clinical trials by the NPCP. Looking at the various single agent trials or in combination with vincristine or cisplatin one can see that the overall response rate in the literature has been low, 0–4% in the U.S. In a recent multicenter American study using different response criteria, activity was nicely demonstrated [34]. In Europe response rates have generally been higher, in the order of 50% [35]. When estracyt was compared to flutamide in a randomized trial, in 220 hormone refractory patients after orchiectomy, no difference was appreciated between the 2 arms. Only 1 PR occured with flutamide; 31% and 26% respectively were stable. Mean survival for both was 48 weeks. Nausea, vomiting, and peripheral edema were more frequent with estracyt [36].

The combination of estracyt + vinblastine, two MAP (microtubular associated protein) inhibitors has recently been studied. The M.D. Anderson, using continuous infusion vinblastine, has reported a 35%–40% RR and other investigators in the U.S. are completing trials and finding approximately a 30% response. Future randomized studies will compare the combination versus either of the single agents.

New agents

Ketoconazole is an oral imidazole derivative with antifungal properties, that inhibits both adrenal and testicular androgen synthesis [37]. The testis seems to be more sensitive than the adrenals to the steroidogenesis blockade of ketoconazole. In unpretreated patients it works rapidly to cut off hormone production, with response in approximately 80%. In hormone-refractory patients the literature is somewhat confusing, as many patients have been simultaneously treated with cortisone [7]. The largest study with 44 patients, reported 1 complete remission (CR) and 5 PR. Stable disease was observed in 25 patients. Pain scores decreased on therapy. The mean benefit was 27 weeks [38]. Trump found that 5 of 36 patients had a greater than 50% decrease in tumor mass or a regression on bone scan after ketoconazole and physiological glucocorticoid therapy [39]. Other studies have poorer results, with response rates <15%. Severe gastric intolerance is the major side effect. Ketoconazole is probably active in soft tissue disease. A definite action is seen in 2–3 months [38–41].

Imidazole R75251 is a novel imidazole derivative active against the Dunning rat. Denis reported that 9/17 (53%) of patients wth bidimensionally measurable parameters had a PR. Moreover, R75251 caused a >50% decrease in PSA levels in 12/24 (50%), with normalization in 2/12 patients. It is well tolerated by the stomach, though some had cutaneous symptoms and muscle fatigue. In contrast to ketoconazole, circulating adrenal androgen levels are not suppressed. Since all patients were castrated, and since the substance doesn't affect the adrenal androgens, an alternative non-endocrine mechanism of action is proposed [42].

Another new agent of interest is suramin, a known antiparasitic agent, has been found to block a number of tumor growth factors. It also inhibits adrenal steroidogenesis, and was first studied in adrenal cancer at the National Cancer Institute (NCI) [43]. The NCI enthusiastically reported high response rates in hormone-resistant prostate cancer, and a flurry of trials was instituted in the U.S. and Europe. Responses are seen above the 300 microgram/ml dose. There may be activity as high as 30%–50% (reduction of PSA) [44]. Weekly blood levels must be obtained both to monitor therapeutic levels of drug and to avoid toxicity. Of interest, the combination of suramin plus interferon gamma may have additive effects in a hormone unresponsive prostate cancer cell line [45].

Radiation therapy

Bone pain is usually associated with metastatic prostate cancer and should be approached systematically. Focal irradiation to palliate bone pain for solitary painful

bone metastases has been supplemented by hemibody irradiation for the palliation of widespread metastases. After allowing for adequate recovery, the alternate half-body may also be irradiated. Side effects include nausea, vomiting, diarrhea, hematologic abnormalities and pneumonitis. In one study, 82% receiving upper hemi-body and 67% receiving lower half-body irradiation remained pain free until death [46]. Strontium-89 has recently been reported effective in palliating bone pain as well. This bone-seeking radionuclide, has high uptake in osteoblastic metastases, and remains in the tumor sites up to 100 days, decaying by beta-particle emission [47]. Strontium produces significant improvement in pain control. An 80% response in patients surviving 3 months after treatment, with 10% completely pain free has been observed and confirmed by several authors [50].

Management of end-stage disease

The management of end-stage prostate cancer patients often requires a multi-disciplinary approach, involving radiation therapists, medical oncologists, nurses and social workers in addition to family members. Pain and symptom relief such as proper analgesics and antimetics in order to palliate end-stage symptoms become crucial issues. Innovative treatment strategies are required if significant impact on overall survival is to be accomplished in the disease. It will be important in the future to identify those patients whose disease is primarily androgen independent. In these, patients alternative treatment might be initiated. If chemotherapy is initiated prior to a decrease in performance status, it may be better tolerated and produce a better response.

Conclusions

Many new approaches to the treatment of hormone-refractory prostate cancer are presently being evaluated. Estramustine alone or in combination, the imidazole derivatives, and suramin have potential. No prospective randomized studies have thus far demonstrated an advantage for a single or combination regimen. For this reason, investigational chemotherapy may be considered first-line treatment. Patient selection coupled with conscientious management of medical problems must be considered when evaluating clinical trials. Clinical trials evaluating new treatment modalities should stratify patients with regards to the known prognostic factors in order to identify those most likely to benefit. The article by Fossa et al. confirm that routine clinical and laboratory data may provide an excellent indication of prognosis. Quality of life evaluations must be included in all future studies.

Cora N. Sternberg, MD, FACP
Regina Elena Cancer Institute
Rome, Italy

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