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Hormonal and Chemotherapeutic Management of Disseminated Carcinoma of the Prostate

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The management of disseminated prostatic carcinoma with hormonal and chemotherapeutic agents is discussed. Hormonal manipulation consists of ablative as well as additive modalities. A new agent, Adriamycin, has shown some effectiveness in selected cases. Significant difficulties are encountered in assessing the objective state of remission of patients undergoing therapy. Further advances through co-operative, randomized clinical trials must be sought. The development of additional chemotherapeutic agents will hopefully expand our horizons.

Medical management of carcinoma of the prostate consists of two main modalities: 1. Hormonal therapy, and 2. Chemotherapy.

Hormonal management may be ablative as in orchiectomy, or additive with diethylstilbestrol, or halotestin stimulation followed by P-32.

When additive hormonal therapy is instituted in patients with disseminated disease, between 80% and 85% of them will experience subjective and/or objective remission. The subjective evidence consists of relief of pain, return of the sense of well-being and relief of anorexia. The objective evidence includes: 1. Return of serum acid phosphatase to normal, 2. Decrease of size and induration of primary tumor by digital examination, 3. Decrease in size and number of demonstrable metastases, 4. Correction of the anemia, and, 5. Weight gain, without edema.

Diethylstilbestrol was formerly administered in the dose of 5 mg, by mouth, daily. Using stilbesterol in this dosage, the Veterans' Administration Cancer Research Group described patients with Stage-IV prostatic carcinoma receiving symptomatic relief but no increase in survival as compared to patients receiving placebo treatment.

An earlier study by the same group demonstrated a marked increase in lethal cardiovascular and thromboembolic disease in patients treated with diethylstilbestrol. More recently Bailer and Byar have shown that 1

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mg of stilbestrol daily is effective in ablating endogenous testosterone production. The VA group have shown that 1 mg diethylstilbestrol daily is as effective in controlling metastatic disease as higher doses without the same toxic cost in cardiovascular, thromboembolic and fluid retention problems.

If the patient enjoys a remission when treated by one hormonal modality and he then undergoes relapse, a second objective remission is not likely to occur when another hormonal agent is used.

In an effort to meet this challenge, many therapeutic efforts have been directed along different avenues. Patients have been treated with testosterone administration followed by P-32, since this isotope is concentrated preferentially in metastatic sites; some palliation has been observed. The testosterone is given for four days followed by P-32 orally, and repeated every four to six weeks, depending on patient response.

Increased dosages of stilbestrol, adrenalectomy, androgens and corticosteroids have all been tried. Prednisone is a good agent and will produce up to 75% subjective remission of variable duration. There is probably no real place for the use of androgens alone. Adrenalectomy or hypophysectomy, in patients with metastatic carcinoma of the prostate, may be helpful. In a combination of ten series with a total of 100 patients, 66% achieved subjective remission following bilateral adrenalectomy while 6% demonstrated objective improvement.

Other forms of chemotherapy have been tried. The newest agent of some promise is Adriamycin, which is a very potent antibiotic, first used in Italy. The probable mode for action is to inhibit the synthesis of DNA. It is usually given at approximately 25 mg/M2 intravenously every three weeks. It produces nausea when administered and depresses the white blood count and platelet counts. Cardiomyopathy is common, particularly if the total dose of 550 mg/M2 is reached or exceeded. The response, if it is to occur, should be seen following the first or second course of chemotherapy.

In patients previously treated with diethylstilbestrol, cardiac toxicity may be more likely to occur and chemotherapy should be discontinued before the total 550 mg/M2 dosage is reached. Total reversible alopecia also occurs,with the use of Adriamycin. (This drug has been found to be effective in some 20-25% of patients, particularly for soft tissue metastases for a median time duration of three months. It is difficult, however, to administer a drug possessing potential cardiac toxicity to elderly males, many of whom have already withstood the hazards of estrogen therapy.)

As clinicians are aware, there is significant difficulty in assessing the objective changes in patients that have disseminated carcinoma of the prostate following trials of various therapeutic modalities. The majority of all osseous lesions are osteoblastic in nature and objective measurement of these is difficult. It is also difficult to measure change in size and consistency of a prostatic nodule from one visit to the next.

The best parameters of therapeutic effectiveness are: 1. returning toward normal of the serum acid phosphatase determinations, 2. the correction of the anemia, and, 3. evidence of weight gain without peripheral edema or ascites.

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