The Turkish Journal of Pediatrics
Volume 26, Nos 1-4, 1984

PROSTATIC CANCER: ENDOCRINE TREATMENT*

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Key words: endocrine treatment L + 1 R + 1 analogues, subcapsular orchidectomy

The standard endocrine treatment for metastatic carcinoma of the prostate is either stilbestrol or orchiectomy. The advantages for either, or both, of these treatments relate mainly to the age and cardiovascular state of the patient. The so-called advantages for (subcapsular) orchiectomy are now accepted. The most common estrogen is stilbestrol: a range of progestogens, antiandrogens and other drugs have been introduced in the hope that they will avoid the undesirable side effects of stilbestrol[1]. More recently, LHRH analogues have been developed and used as alternatives to stilbestrol. These agents are still in the development and assessment stage but some useful observations can now be made. It has been suggested that suppression of testicular androgens should be combined with adrenal suppression.

It has long been hoped that it would be possible to identify those patients (approximately 20%) who do not respond to endocrine treatment. The most promising method using receptor protein analyses has proved to be of very limited practical value and some alternate methods under study deserve attention.

Estrogen / castration treatment is almost inevitably followed by relapse or "escape" at a later date. The reasons for this escape from treatment are debatable but the essential concept is that androgen-independent prostatic cancer cells exist and eventually become dominant. The use of chemotherapeutic agents together with endocrine drugs is the oretically attractive; these may be given either as a combined preparation (e. g. estrogen + nitrogen mustard) or separately.

For the patient who has failed primary endocrine treatment, further endocrine manipulation is of very limited value. There are no significant objective benefits from the use of different estrogens or of larger doses of estrogens. Castration after failed estrogen treatment has no benefit for the patient[2]. Other hormones such as progestogens and anti-androgens have some affect but usually for anly a short duration.

The monitoring of response to treatment by these patients on hormones and chemottherapeutic agents is difficult and can often lead to misleading interpretations.[3]

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Surgical adrenalectomy has been discarded because of the disappointing results. Medical adrenalectomy using aminoglutethimide continues to be used but again the results are disappointing and side effects of nausea and vomiting are common. Hypophysectomy is usually reserved for the patient with widespread pain that cannot be controlled by drugs or by radiotherapy. The response rate may be as high as 80% but there is no effect on survival[4].

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DISCUSSION

Akdaş: I wonder if Mr. Smith could share his knowledge of LHRH analogues with us.

Smith: Well, I don't reckon to be an expert on LHRH, but I did go to a meeting on the subject in Rotterdam, and I have used the ICI depot.

At the moment Buserelin® , Luprolide® and Zoladex® are all available. Buserelin, made by Hoechst, can be given either up the nose or by a daily injection subcutaneously. Luprolide, made by Abbott is given as a daily subcutaneous injection and Zoladex made by ICI, can be injected subcutaneously daily but there is also a depot preparation which lasts for one month.

The makers are very anxious to develop a market for these products. The German firm of Hoechst wants to get a phase III trial going of Buserelin versus anything, orchidectomy for instance. There seems to be no problem connected with administering this drug but in some cases there is clinical data showing a problem of escape, that is rising plasma testosterones after a period of time despite continuing therapy.

The users of Luprolide have so far shown no escape. Zoladex, given subcutaneously, has been shown to have a tendency to escape in three patients all from the same center; but there has so far been no evidence of escape with the depot product which is given at a dose of 3.6 mg every 30 days. ICI are now carrying out

phase I studies on Zoladex. One hundred and four patients at seven centers in Europe are being given doses of 0.9 mg, 1.8 mg and 3.6 mg, injected subcutaneously monthly, by a nurse. The drug dissipates itself within 30 days. So far there has been no evidence of escape. As yet there is no clinical information on the effect of remission with this agent, with the depot, though there is evidence of clinical remission of the orchidectomy or stilbestrol rate with the other agents. So ICI is now anxiously obtaining phase II information before doing a phase III trial. They want to determine that this product is not only endocrinologically satisfactory but also clinically satisfactory.

So that's the state of the market today. People who have used these products reckon that these are no side effects expect for reduced libido and impotence; that it is probably the same as an orchidectomy.

Akdaş: What I would like to ask first is, how frequently do you think we should do the bone scan? Every three months, every six months or yearly?

Smith: I think it depends; if you're in clinical practice, then it is nice to have a bone scan once, to know whether your patient is metastatic or not. I don't think it's essential, but I think it's useful. When you have done it once, and you have decided how you are going to treat that particular patient, then I think you can treat him as decided and I don't think you need to see him again until such time as he has further symptoms, relating either to his primary or possibly to his metastases. So I don't think you need a second bone scan at all, unless you want to know what the outlook is for the patient.

Chisholm: I think a bone scan is essential at diagnosis. Otherwise you can't classify your patient.

Akdaş: It was really the follow-up of the patient I had in mind.

Chisholm: Yes. But that's your baseline. If we had good second line treatment that we could use when we detect progression, then a bone-scan would be handy. But at the moment we don't have good second line treatment, and we only change the treatment when symptoms necessitate it; so it's only a matter of academic interest.

Akdaş: If I understand your comments on this correctly, the clinical response to Buserelin and the other drug, is the same as it would be to DES and orchidectomy.

Barlas: What do you think about the effects of DES diphosphate?

Chisholm: I think it's practically effective, but I don't know that I think it has any great advantages. You know there have been some reports recently that TUR's for carcinoma of the prostate worsen the prognosis. I'm not really sure that I believe that because I think the patients who receive TUR are a selected group. The very fact they have a TUR means they have some other problem of obstruction.

Türkyılmaz: How do you treat pains in the bone?

Chisholm: We use a lot of radiotherapy and analgesics; and for a period we were interested in some of these anti-inflammatory drugs, for mild pain they are really good, just as they are for treating arthritis.

Wickham: I find steroids are often quite helpful. A dose of prednisone or something like that helps people with secondary relapse.

Smith: And if that doesn't, mitomycin-C is the drug which is probably the best.

Erözenci: If the tumor has invaded the external sphincters what do you do?

Chisholm: There's nothing to do. I really don't think you can seriously offer them an artificial sphincter, if that's what you're driving at; that's what I would call exotic urology, and I don't seriously think that there's a place for expensive sphincter work.