HORMONAL THERAPY OF PROSTATIC CARCINOMA: IS THERE A RATIONALE FOR DELAYED TREATMENT?

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The report by Huggins and Hodges in 1941 that endocrine manipulation caused a decrease in acid phosphatase dramatically changed the treatment of metastatic prostatic cancer. Since that time, case reports have clearly described objective responses to hormonal manipulation of this disease. Nevertheless, although it is generally accepted that hormonal therapy produces subjective remissions in a large proportion of patients with symptomatic metastases, controversies remain regarding the effect of hormonal manipulation on survival and the timing of therapy, i.e., should treatment be started at the time of the initial diagnosis of metastatic disease or at the onset of symptoms.

The question of whether or not hormonal therapy actually improves survival can be addressed from both basic science and clinical perspectives. Animal models have consistently demonstrated that endocrine manipulation causes growth inhibition of the hormone sensitive Dunning R-3327-H and R-3327-G rat prostatic adenocarcinomas. However, despite the beneficial effect of hormonal manipulation in this model, continued treatment does not prevent tumor relapse. Tumor regrowth is associated with an increase in the aneuploid cell population approaching the control level.

Isaacs and Coffey have demonstrated that the hormonally sensitive Dunning R-3327-H adenocarcinoma contains both androgen dependent and independent tumor cells. The finding that this tumor continues to demonstrate hormone responsiveness, without cure, despite multiple passages provides evidence that the growth rates of the hormone sensitive and resistant cells are similar, because, if one cell type had a significant growth advantage over the other, extended in vivo passage would be associated with the elimination of the other cell type.

The differences between androgen sensitivity and androgen resistance may be quantitative as well as qualitative. Orchiectomy results in irreversible progression to a hormone insensitive state in the R-3327-H model of prostatic carcinoma. The situation is different with the R-3327-C cell line which is poorly differentiated but hormonally sensitive. Pollack and associates have demonstrated that both orchiectomy and hormonal therapy decrease the tumor growth rate compared to intact rats. In their model, diethylstilbestrol had a greater effect on tumor cell growth than orchiectomy, and orchiectomy suppressed but did not eliminate tumor cells that were hormone responsive. These experiments suggest that three cell types can be functionally defined: hormone dependent cells which require androgen for survival; hormone sensitive cells which grow faster in the presence of androgen; and hormone independent cells which are unresponsive to androgen. The response of prostate cancer to hormonal manipulation depends on the distribution of these three cell types and their growth rates.

There is relatively little information available regarding human prostatic adenocarcinomas except for clinical data. Human prostatic tumors are often heterogeneous and probably contain a mixture of both hormonally sensitive and insensitive cells. However, most of the human prostate cancer cell lines that have been established have limited hormone sensitivity. An exception is PC82, a hormone responsive human prostatic carcinoma that is serially transplantable in athymic nude mice.

FIGURE 1. Response of lymphatic metastases to hormonal therapy. (A) Pelvic CT (12/29/82) demonstrating a dilated left ureter (curved white arrow) and enlarged left pelvic lymph nodes (straight black arrows). Bilateral orchiectomy was performed January 3, 1983. (B) CT (5/3/83) demonstrating a marked decrease in the size of the lymphatic metastases. (C) CT (10/18/83) showing resolution of hydronephrosis.

does not form tumors in female nude mice, and castration of tumor-bearing male mice results in a decrease in tumor volume. Similar, precise documentation of tumor behavior in patients with prostatic carcinoma is scarce. However, it is now possible to obtain it with newer diagnostic techniques. Computed tomography can be used to demonstrate changes in soft tissue metastases that are otherwise difficult to quantify (Fig. 1).

Prospective randomized studies of hormonal therapy in man by the Veterans Administration Cooperative Urological Research Group has not clarified the role of hormonal therapy. Several problems with these studies make the interpretation of the data difficult. First, the use of high doses of estrogen (diethylstilbestrol) in some trials was associated with an excess of cardiovascular deaths, and, second, patients in the control group in whom progressive disease developed were frequently given hormonal therapy. As a result of this, the lack of difference of survival between the control and estrogen therapy groups may represent similar survivals between patients treated with either immediate or delayed hormonal treatment rather than a failure of hormonal manipulation to improve survival.

Barnes has reported on a large nonrandomized group of patients with low-stage prostate cancer who had either immediate or delayed therapy. His data suggest that long-term
FIGURE 3. Results of hormone manipulation of prostatic carcinoma. Dashed horizontal line represents onset of symptomatic metastases. Curves a, b, and c represent 1, 2, and 3 log kills, respectively.

The natural history of prostatic cancer can be evaluated by analysis of tumor cell growth. Stamey has reported a model of prostatic carcinoma which appears to mirror clinical tumor behavior (Fig. 2). Although the tumor doubling time in vivo is unknown, the model is useful for the analysis of hormonal therapy. Two assumptions will be made in this evaluation. First, the growth of prostatic cancer as a solid tumor will follow Gompertzian kinetics after a tumor volume of 1 ml is reached. Second, prostatic neoplasms are composed in varying proportions of hormonally sensitive and insensitive cells with similar doubling times.

Figure 3 demonstrates what one may reasonably expect after hormonal manipulation of a prostatic neoplasm. The top curve represents an untreated neoplasm or one in which no hormonally sensitive cells are present. When hormonal manipulation is begun, the degree of response will depend on the proportion of hormonally sensitive cells in the population. Obviously, if the neoplasm was composed entirely of hormone dependent cells, hormonal manipulation would result in a complete disappearance of the tumor. Various intermediate stages are demonstrated by the lines representing 1, 2, and 3 log kills (90%, 99%, and 99.9% of the cells killed, respectively). The horizontal line represents an arbitrary point at which symptomatic metastases are present. The interval of time between initiation of therapy and regrowth of neoplasm to this horizontal line is the period of remission. In this model, the duration of response to therapy correlates with the degree of log kill and with potential survival. The obvious conclusion is that the greater the proportion of hormonally sensitive cells in an individual neoplasm, the greater the log kill and, therefore, the longer the duration of remission and survival.

Figure 4 demonstrates the effects of early and late hormonal therapy. If the doubling times of both hormonally sensitive and insensitive cells are similar, the proportion of these cells in the survival with delayed hormonal therapy is no worse and possibly better than that obtained with immediate treatment. Because of the long natural history of this disease and undefined clinical variables, the precise impact of hormonal therapy has not been adequately determined. Nevertheless, the fact that up to 90 percent of the patients have either objective remission or stabilization of their disease after hormonal manipulation is strong evidence for the clinical effectiveness of hormonal therapy. In fact, documented objective remissions clearly show that in some cases hormonal therapy alters the natural history of the tumor and probably prolongs survival. Given the effective nature of this treatment, can delayed therapy be justified?
FIGURE 5. Effect of delayed hormone manipulation. (A) Patient whose hormone sensitive cells are growing faster than hormone insensitive cells. With delayed hormone therapy cell kill is greater because of increased numbers of hormone sensitive cells. This is accompanied by longer time to reach $10^{12}$ cells. (B) Patient whose hormone sensitive cells are growing slower than hormone insensitive cells. Curves a and b represent 1 and 2 log cell kills, respectively. Delayed therapy (dotted curve) is less effective (0.5 log kill) because of fewer numbers of hormonally sensitive cells. Nevertheless, because of growth kinetics, effect of decreased numbers of hormonally sensitive cells on delayed therapeutic efficacy is blunted.
the survival from the time of therapy (orchietomy) continues to fall dramatically with age, the absolute survival in years increases with the age at orchiectomy (Fig. 6). As the authors appropriately point out, multiple variables may have a role in this phenomenon. Nevertheless, this does suggest that the clinical situation which physicians encounter is much more complicated than that associated with the Dunning model and that absolute survival is an important consideration.

The advantage of the proposed model is that it is theoretically testable. Although hormonally sensitive and insensitive cells cannot be accurately characterized through conventional histology, newer methods of defining hormone sensitive cells may be able to demonstrate whether this hypothesis is correct. Prostatic nuclear androgen receptor content can be measured on tissue obtained by needle biopsy and correlates with response to hormonal therapy. Androgen binding by histochemical assay also correlates with hormone responsiveness. Serial biopsies in patients using such techniques could be used to assess whether or not the model is a correct one. In addition, methods which are more sensitive and direct for determining hormonally sensitive cells may yet be developed. If, for example, monoclonal anti-bodies are produced that can differentiate hormone sensitive from hormone insensitive cells, then tumor cells could be quickly and easily characterized by the use of flow cytometry.

Although much remains to be learned about the biology of prostatic cancer, both research and clinical data offer support for the proposed model. Important unknown variables such as the growth rate and hormone responsiveness of metastatic deposits remain to be defined. Nevertheless, this relatively simple model provides a means to study this challenging neoplasm. If the model can be verified or disproved, then the timing of hormonal therapy for patients with prostatic cancer would be placed on a more rational basis.

References

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