Importance of Continued Testicular Suppression in Hormone-Refractory Prostate Cancer

By C.D. Taylor, P. Elson, and D.L. Trump

Purpose: Patients in whom prostate cancer progresses despite testicular androgen ablation are generally said to have cancers that have become resistant to hormonal maneuvers. If androgen suppression has been pharmacologic, this therapy is often stopped before consideration of other systemic treatments. This exploratory study sought clinical correlates of experimental evidence that there may be substantial acceleration of tumor growth after cessation of androgen suppression.

Materials and Methods: A retrospective multivariate analysis was performed on survival data for 341 patients treated on four clinical trials of secondary therapy for hormone-refractory prostate cancer. Factors included in the model were recent weight loss, age, performance status, disease site (soft tissue vs bone-dominant), prior androgen therapy, and continued androgen suppression vs discontinued exogenous endocrine therapy.

Results: Recent weight loss, age, performance status, and disease site were important prognostic factors for survival duration in hormone-refractory prostate cancer. Correcting for these factors, continued testicular androgen suppression was also an important predictor of survival duration in all data sets examined.

Conclusion: This retrospective study showed a modest advantage in survival duration for men with hormone-refractory prostate cancer who continued to receive testicular androgen suppression. The hypothesis that continued hormonal maneuvers can still affect survival in this group warrants examination in prospective trials.


Most patients with metastatic prostate cancer will benefit from suppression of testicular androgen secretion. Orchiectomy and luteinizing hormone-releasing hormone (LHRH) analogs or pharmacologic doses of estrogen are considered to be equivalent in terms of response and time to treatment failure. There is evidence that the combination of LHRH analog and the antiandrogen flutamide results in superior survival durations.

When patients treated with initial hormone therapy experience progression of disease, they are usually considered to have androgen-insensitive tumors. Those patients who have not undergone orchiectomy often discontinue the primary exogenous hormone treatment. However, the Dunning rat prostate cancer model cell lines, which are relatively insensitive to androgens in vitro and grow slowly in the castrated host, can grow more rapidly in an intact host. Human trials also indicate that some tumor cells in hormone-refractory patients retain sensitivity to plasma androgens. The possible regrowth of cells that retain androgen sensitivity when testicular suppression ceases may confound clinical trials of secondary therapy, and has been of concern to some investigators. Jones has presented arguments against continued endocrine therapy, and contends that exogenous hormones must be stopped before beginning investigative agents. However, we have found no studies that specifically address this question; there is no standard approach to testicular androgen suppression in individuals with intact testes in whom prostate cancer progresses despite initial hormone treatment. Trials of cytotoxics conducted by the National Prostate Cancer Project (NCPC) after 1975 required prior orchiectomy, and phase II and III trials of the Eastern Cooperative Oncology Group (ECOG) since 1980 have either recommended or required continuous testicular androgen suppression. Our literature review of 25 other trials shows that approximately 20% of patients enter such studies without prior orchiectomy. The management of testicular androgen secretion in these trials was specified in less than 10% of the studies reviewed.

To evaluate the impact of continued testicular androgen suppression, we have retrospectively reviewed survival data from four clinical trials in refractory prostate cancer, from the ECOG and the University of Wisconsin.

Materials and Methods

Three data bases were analyzed for differences in survival between men with hormone-refractory prostate cancer who continued testicular suppression (either medical or surgical) as they began investi-
gential and those with intact testes who had ceased medical testicular androgen suppression as they began the new treatment. Eligibility criteria for these trials were comparable: histologic diagnosis of prostate cancer; documentation of progression despite primary therapy; adequate hematologic, renal, cardiac, and hepatic function; adequate performance status (ECOG 3 or better); no exposure to test agents; and informed consent. Survival was the primary end point considered in this investigation, and was measured from the date of registration on study to the date of death, or the date last known alive. In patients with such short survival, most deaths were probably cancer related. Information on specific causes of death was not available. Survival for individual prognostic factors was estimated using the Kaplan-Meier method and comparisons were made using the log-rank test. A Cox proportional hazards regression model, stratified by treatment and study if more than one clinical trial was being examined, was used to analyze simultaneously the effect of continued androgen suppression and a number of other potential prognostic factors. The factors included in the model were hormonal status or treatment (ie, continued androgen suppression vs discontinued exogenous endocrine therapy), initial performance status (ambulatory vs not ambulatory), weight loss in the preceding 6 months (< 5% of body weight vs ≥ 5%), age (≥ 65 years vs > 65 years), prior treatment with radiotherapy (no vs yes), and disease site (measurable or assessable vs bone-dominant disease). These latter potential prognostic factors were suggested by a prior analysis of ECOG data and must have been recognized elsewhere also. The effect of continued androgen suppression was evaluated within this model using the likelihood ratio test. In addition, patients treated on the protocols discussed in this report, but excluded from the analyses, were compared with the analyzed cases to determine if there were any significant differences with respect to survival duration. The groups were comparable, with a median survival duration of 6.6 months for the excluded cases and 7.9 months for the analyzed patients ($P = .29$).

Data from four clinical trials were analyzed in three groups (Table 1).

### Group No. 1

Protocol EST 3882 randomized men with progressive cancer to receive either doxorubicin (50 mg/m² intravenously [IV] every 3 weeks) or the same doxorubicin dose plus diethylstilbestrol diphosphate (1 g IV daily for 5 days, then twice weekly). One hundred eighty-eight men were entered onto this study, 165 of whom are included in this report. Twenty-three patients were excluded, primarily because they failed to meet the eligibility criteria of the original trial. Guidelines for EST 3882 suggested that prior exogenous hormone therapy be stopped, but this was not specifically required; when records were reviewed to determine which patients had discontinued prior exogenous hormone therapy, two patients assigned to the doxorubicin-alone arm were found to have continued exogenous hormones while on protocol.

For the purposes of this report, the 165 analyzed cases were divided into three patient groups: doxorubicin patients who did not have orchiectomy and either discontinued or probably discontinued exogenous hormones before entering the trial ($n = 23$), doxorubicin patients who had orchiectomy ($n = 55$) or continued exogenous hormones ($n = 2$), and patients assigned to receive doxorubicin and diethylstilbestrol diphosphate ($n = 85$). When data from this analysis proved interesting, the following additional sources were reviewed for confirmation.

#### Group No. 2

All patients entered onto EST 2373, a previously published randomized comparison of doxorubicin and fluorouracil for hormone-refractory prostate cancer, and EST P-E883, a phase II study of carboplatin in similar patients, were grouped according to hormonal status and studied. Exclusions from the 196 patients initially considered for this part of the analysis are listed in Table 1. Sixteen patients were ineligible for the original therapeutic study, and incomplete or no data were available for another 23. In addition, 19 patients entered onto EST 2373 were excluded because they had received no hormonal therapy at all before entering the trial, leaving 138 patients available for analysis.

#### Group No. 3

University of Wisconsin Clinical Cancer Center Study C08586 studied the use of ketoconazole 400 mg every 8 hours with hydrocortisone 40 mg/d in divided doses. Thirty-eight patients were studied, and serial testosterone and gonadotropin serum levels were measured. The nine patients who had not undergone orchiectomy were required to stop exogenous hormones. The patient information

### Table 1. Case Status

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No. Entered</th>
<th>Exclusions*</th>
<th>No. Analyzed</th>
<th>Orchietomy or Continued Hormones While On-Study</th>
<th>No Orchietomy and Discontinued Exogenous Hormones</th>
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<tbody>
<tr>
<td>E3882</td>
<td>Doxorubicin</td>
<td>92</td>
<td>12</td>
<td>80</td>
<td>57</td>
<td>23</td>
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<tr>
<td></td>
<td>Doxorubicin + diethylstilbestrol diphosphate</td>
<td>96</td>
<td>11</td>
<td>85</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>E2373</td>
<td>Doxorubicin</td>
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<td>34</td>
<td>78</td>
<td>65</td>
<td>18</td>
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<tr>
<td></td>
<td>Fluorouracil</td>
<td>54</td>
<td>21</td>
<td>33</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>PE883</td>
<td>Carboplatin</td>
<td>30</td>
<td>3</td>
<td>27</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>C08586</td>
<td>Ketoconazole</td>
<td>38</td>
<td>0</td>
<td>38</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td>422</td>
<td>81</td>
<td>341</td>
<td>287</td>
<td>54</td>
</tr>
</tbody>
</table>

*Includes unknown hormone status. E2373: doxorubicin, $n = 4$; fluorouracil, $n = 3$; PE883: $n = 1$.

*Includes 10 patients who continued exogenous hormones while on-study. E2373: doxorubicin, $n = 5$; fluorouracil, $n = 1$; PE883: $n = 2$; E3882: doxorubicin, $n = 2$.
needed to do the multivariate analysis described earlier was not available and therefore only an unadjusted comparison by orchiectomy status was performed in this group.

No data were available in any of these sets about whether total or subcapsular orchiectomy had been used, and no comment can be made regarding the debatable difference between the procedures.15,16

RESULTS

Table 2 lists the distribution of the key prognostic factors analyzed in this report, excluding the ketoconazole study. With the exception of prior radiotherapy in group no. 2, there were no serious imbalances with respect to any of these factors and hormonal status. In group no. 2, 20 of 22 patients (91%) who discontinued exogenous hormones had been treated previously with radiation, compared with only 79 of 116 (68%) who had had orchiectomy or continued exogenous hormonal therapy while on study \((P = .04, \text{Fisher's exact test})\). Multivariate analysis in these patient groups showed that performance status, recent weight loss, age, and disease site do indeed affect survival duration. Furthermore, in both groups of patients, cessation of exogenous endocrine therapy in nonorchiectomized men was associated with a decrease in survival duration after adjusting for the other factors in the model. Unadjusted findings were similar in the ketoconazole study.

**Group No. 1 (EST 3882)**

Survival durations in the two prospectively randomized therapy groups, doxorubicin and doxorubicin plus diethylstilbestrol diphosphate, were similar (median survival durations, 7.8 and 8.5 months, respectively; \(P = .53\)). However, there was some indication that patients without orchiectomy who were randomized to receive doxorubicin alone and who stopped prior exogenous endocrine therapy had shorter survival times (median, 6.6 months) than those with prior orchiectomy randomized to receive doxorubicin alone (median, 10.1 months; \(P = .06\)) and those receiving doxorubicin plus diethylstilbestrol diphosphate without prior orchiectomy (median, 8.5 months; \(P = .10\)) (Fig 1). Multivariate analysis, which included the five other prognostic factors mentioned earlier, did not change these figures. In addition to continued androgen suppression, little or no recent weight loss \((P = .01)\), age \(\leq 65\) years \((P = .03)\), and ambulatory status \((P = .12)\) were also associated with improved survival duration.

**Group No. 2 (EST 2373 and EST P-E883)**

There was no statistically significant survival difference between patients who continued androgen suppression and those who did not in the unadjusted analysis (median survival times, 7.3 and 5.6 months, respectively; \(P = .44\)). However, after adjusting for the effects of the factors included in the multivariate analysis, patients who had continued androgen suppression had significantly better survival durations than the nonorchiectomized patients who discontinued their exogenous hormones \((P = .04)\). Lack of significant weight loss \((P = .004)\), age \(\geq 65\) years \((P = .07)\), good performance status \((P < .001)\), and bone-dominant disease \((P = .02)\) were also seen to be associated with longer survival duration.

**Group No. 3 (CO 8586)**

Survival duration was superior for orchiectomy patients (9.9 months) compared with patients who had prior diethylstilbestrol or LHRH analogs discontinued on entry into the study (3.6 months; \(P = .01\)) (Fig 2). In three of nine patients who had not undergone orchiectomy before entry, plasma testosterone concentrations well above the castrate level were documented during the course of ketoconazole administration.

DISCUSSION

Since the demonstration in 1941 by Huggins et al17 that orchiectomy improved bone pain in metastatic prostate cancer, numerous therapies have been used for symptom control. However, overall effect on survival duration has been debated. The survival advantage demonstrated for 1 mg/d of diethylstilbestrol over placebo and other dose levels after prolonged follow-up in the clinical trials of the Veterans Administration Cooperative Urological Research Group1 has not been widely emphasized or accepted.

The data presented here are enticing in that a consistent survival advantage to continued testicular androgen suppression was found. This suggests that recovery of testicular androgen synthesis to a level adequate to stimulate prostate cancer growth, even in hormone-refractory patients, is possible. The recent data on survival superiority for total androgen ablation18 as demonstrated by randomized study of the LHRH analog leuprolide with or without the antiandrogen flutamide1 also suggests that small amounts of circulating androgens may be important in the natural history of prostate cancer, a concept being further explored in a large intergroup study of orchiectomy randomized with or without flutamide.

There is no standard therapy for patients in whom prostate cancer progresses despite suppression of testicular androgen synthesis. Reports of secondary hormonal therapies, including both antiandrogens19,21 and adrenal steroidogenesis inhibitors,22,23 and of cytotoxic drugs,24-26 give modest objective response rates and no convincing evidence of improved survival duration.
Patients in whom prostate cancer progresses despite testosterone androgen suppression are generally felt to have cancers that have become hormone-resistant, and treatment with exogenous androgen suppression, such as estrogens or LHRH analogs, is often stopped when progression occurs. However, there is evidence against complete hormone independence of these cancers. In animal models, it is possible to demonstrate cells that are androgen-independent, androgen-sensitive, and androgen-dependent. One might therefore spec-

Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>EST 3882</th>
<th></th>
<th>EST 2373 and PE 883</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doxorubicin, No Orchiectomy, and Discontinued Exogenous Hormones</td>
<td>Doxorubicin and Diethylstilbestrol Diphosphate</td>
<td>No Orchiectomy and Discontinued Exogenous Hormones</td>
</tr>
<tr>
<td>No. of patients</td>
<td>23</td>
<td>57</td>
<td>85</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>6.5</td>
<td>10.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Performance status (%)</td>
<td>Ambulatory: 43</td>
<td>63</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Not Ambulatory: 57</td>
<td>37</td>
<td>46</td>
</tr>
<tr>
<td>% body weight lost in previous 6 months (%)</td>
<td>&lt; 5: 61</td>
<td>68</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>≥ 5: 39</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>Disease site (%)</td>
<td>Soft tissue: 26</td>
<td>42</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Bone dominant: 74</td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td>Age, years (%)</td>
<td>&lt; 65: 65</td>
<td>47</td>
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<tr>
<td></td>
<td>&gt; 65: 35</td>
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<td>Prior radiotherapy (%)</td>
<td>No: 17</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Yes: 83</td>
<td>70</td>
<td>74</td>
</tr>
</tbody>
</table>

Fig 1. Survival by treatment for ECOG study E3882. (---) Doxorubicin, no orchiectomy, and exogenous hormones discontinued before study entry, n = 22/23 failures; (-----) doxorubicin, orchiectomy, or exogenous hormones continued while on-study, n = 56/57 failures; (-----) doxorubicin plus diethylstilbestrol diphosphate, n = 80/85 failures.

Fig 2. Survival on Wisconsin Clinical Cancer Center study C08586. (---) No orchiectomy and exogenous hormones discontinued before study entry, n = 9/9 failures; (-----) orchiectomy, n = 26/29 failures.
ulate that cessation of androgen suppression, with the attendant if irregular recovery of androgen production, might allow accelerated tumor growth.

There is indirect clinical evidence for this theory. Manni et al studied exogenous androgens as a means of priming prostate cancer to increase the efficacy of cytotoxic chemotherapy in hormone-refractory patients, but found that the patients receiving androgens had shortened survival and, often, exacerbated symptoms. Fowler and Whitmore also found unfavorable responses in patients given exogenous testosterone, actually more so in relapsing patients than in patients who were untreated or in remission. The NCPC, in studies after 1975, required all patients entering second-line cytotoxic drug trials to have undergone orchiectomy because of concern about reactivation of an androgen-sensitive tumor-cell population, but they did no formal analysis of their earlier studies to confirm this hypothesis (Murphy GP, personal communication, 1988).

In this retrospective analysis, we have demonstrated in three separate data subsets that continued androgen suppression is associated with prolongation of survival in men whose prostate cancer is progressing despite primary endocrine therapy. A median survival advantage of 2 to 6 months is associated with either exogenous hormone suppression or with orchiectomy. The uniformity of our exploratory results among the three data sets is highly suggestive. Clearly, all such retrospective analyses must be interpreted with caution. We are unaware of other data sets that have been subjected to such analysis. Definitive exploration of this hypothesis would require a prospective randomized trial of continuous suppression of testicular androgen synthesis compared with cessation of such treatment in nonorchiectomized patients with hormone-refractory disease. Lacking the results of such a study, clinicians caring for patients with hormone-refractory prostate cancer should consider the wisdom and necessity of stopping testicular suppression therapy. Although the survival difference seen here is modest, the hypothesis that a tumor clone retaining complete or partial sensitivity to a failed therapy might rebound with enough speed to change prognosis has both biologic and practical clinical implications.

REFERENCES

27. Tannock IF: Is there evidence that chemotherapy is of benefit to patients with carcinoma of the prostate? J Clin Oncol 3:1013-1021, 1985