Relationship between Tumor Size and Curability of Prostatic Cancer by Combined Chemo-Hormonal Therapy in Rats

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ABSTRACT

Nearly all men with metastatic prostatic cancer respond to androgen ablation, demonstrating that at least a portion of their cancer cells are androgen responsive. Unfortunately, however, individual prostatic cancers contain clones of androgen-independent, in addition to androgen-responsive, cancer cells. Due to this tumor cell heterogeneity, essentially all patients treated with androgen ablation alone eventually relapse to a state unresponsive to further antiandrogen therapy; cures are rarely produced. To produce cures, additional nonhormonal therapy targeted at the androgen-independent prostatic cancer cells within the patient should be combined with androgen ablation targeted at the androgen-dependent cancer cells.

The validity of such combined chemo-hormonal therapy was tested using, as the experimental model, two members of the Dunning system of serially transplantable rat prostatic cancers. Specifically the slow growing, well differentiated H and the fast growing, poorly differentiated G Dunning sublines were used, since these cover the clinical extremes observed for human prostatic cancers. The chemotherapeutic agent used in combination with surgical androgen ablation (i.e., castration) in these studies was Cytoxan. These studies demonstrate that for both the H and G cancer-bearing rats, the mean survival following combined chemo-hormonal therapy was increased above that found for castrate or Cytoxan when either was used as monotherapy. In addition, an inverse relationship between tumor size at the time of initiation of therapy and the ability of the combined chemo-hormonal therapy to cure animal bearing either the H or G sublines was demonstrated. Such combined chemo-hormonal therapy could only cure a proportion (i.e., 30–40%) of H or G tumor-bearing animals if initiated when the tumor was ≤0.2 cm³ in size. In contrast, if the tumor was 1–2 cm³ in starting size when the chemo-hormonal therapy was initiated, no animal was cured. Neither of the monotherapies (i.e., castrates or Cytoxan alone) could cure any animals regardless of the starting size.

INTRODUCTION

The annual death rate from prostatic cancer has not decreased at all over the subsequent 40 years since androgen withdrawal has become standard therapy (1). Over the last 40 years, the superficially benign nature of androgen withdrawal therapy has tended to disguise the fact that metastatic prostatic cancer is still a fatal disease for which no therapy is available which effectively increases survival (2). Nearly all men with metastatic prostatic cancer treated by androgen ablation do respond, demonstrating that at least a portion of their cancer cells are androgen responsive. Unfortunately, however, essentially all of these patients eventually relapse to a state unresponsive to further antiandrogen therapy, no matter how aggressive their secondary treatment (3–5).

Studies by a series of laboratories have demonstrated that a major reason for this universal relapse of metastatic prostatic cancer to androgen ablation is that prostatic cancers are heterogeneously composed of clones of both androgen-dependent and -independent cancer cells even before hormone therapy is begun (6–9). Development of such tumor cell heterogeneity can occur by a variety of mechanisms (e.g., multifocal origin of the tumor, adaptation, or genetic instability) (10). Regardless of the mechanism of development of such cellular heterogeneity, once androgen-independent cancer cells are present within individual prostatic cancers, the tumor is no longer curable by androgen withdrawal therapy alone, no matter how complete, since this therapy kills only the androgen-dependent cells without eliminating preexisting androgen-independent prostatic cancer cells.

Theoretically, to effect all of the heterogeneous prostatic cancer cell populations within an individual cancer, effective nonhormonal chemotherapy specifically targeted against the preexisting androgen-independent cancer cells should be combined with androgen ablation targeted at the androgen-dependent cancer cells. Animal models have clearly demonstrated not only the fact that prostatic cancer can be heterogeneously composed of androgen-dependent and -independent prostatic cancer cells before hormonal therapy is begun (8, 9), but also the fact that an increase in survival above that produced by castration alone cannot be produced no matter how complete the androgen withdrawal therapy utilized (11–13). Using these animal models and Cytoxan as a model chemotherapeutic agent, it has been demonstrated that: (a) When either androgen ablation or Cytoxan chemotherapy are given as monotherapy, they are both most effective when given as early as possible; (b) when androgen ablation is combined with Cytoxan chemotherapy it is most effective when both therapies are begun simultaneously not sequentially and as early as possible; and (c) when androgen ablation and Cytoxan treatment are begun simultaneously and early, it is possible to increase survival above that found for either treatment when given optimally as single modalities (i.e., such simultaneous early treatment enhances the individual therapeutic effectiveness of both treatments) (14).

While an enhanced effectiveness of such combined chemo-hormonal therapy has been demonstrated with regard to overall host survival, no animal was cured in these previous studies. Recently, the relationship between tumor size and curability of metastatic prostatic cancer by surgery plus adjuvant chemotherapy has been studied in this same Dunning system of serially transplantable rat prostatic cancers (15). These studies have demonstrated that cures are not obtained if combined therapy is begun too late in the course of disease (i.e., too great a tumor burden). Cures can be reproducible in high frequencies only by treating as early as possible, when the tumor burden is low (15). Based upon these data, the present studies were undertaken to examine if there is also an inverse relationship between tumor size and curability of prostatic cancer by combined chemo-hormonal therapy. As a test system, two of the members of the Dunning system of serially transplantable rat prostatic cancers were used as a model. Specifically, the slow growing, well-differentiated H and the fast growing, poorly differentiated G sublines were studied since both of these sublines are androgen responsive (11) and these sublines cover the clinical extremes observed with human prostatic cancers, and neither of these sublines is curable by hormone therapy alone, no matter how extensive (11).
MATERIALS AND METHODS

Animals. Inbred male Copenhagen (Cop) rats (i.e., 150–200 g) were obtained from Harlan Sprague Dawley (Indianapolis, IN). The history of the development of the Dunning R-3327 H and G rat prostatic cancer sublines has been described in detail previously (16). The H and G sublines were separately removed from an individual male Cop donor rat bearing the appropriate S. Q. tumor in the flank when 2–3 cm³ in size. The donor tumors were cut into trocar pieces (~10 mg) and placed in Hank's balanced salt solution until transplanted into the experimental recipient animals. Recipient male rats were anesthetized with Metofane (methoxyflurane; Pitman Moore, Washington Crossing, NJ). The trocar pieces were then placed s.c. in the flank of male Cop rats by making a 1-cm incision, separating the s.c. connective tissue with blunt dissection, and placing the tumor s.c. The incision was closed with the use of skin clips (autoclips, 9 mm; Clay Adams, Parsippany, NJ).

Animal Treatment. When indicated, castration was performed by a scrotal incision under Metofane anesthesia. The chemotherapeutic agent chosen for the present study was Cytoxan (cyclophosphamide). Cytoxan was dissolved in physiological saline (0.9% sodium chloride) and given i.p. at a dose of 90 mg/kg body weight. Antibiotic was provided in the drinking water of all animals for the purpose of protecting against hemorrhagic cystitis secondary to cytoxan toxicity and to prevent any death due to secondary infection during the immunosuppression period (determined to be approximately 10 days) induced by each injection of cytoxan. Preliminary studies demonstrated that treatment of all animals with the prophylactic antibiotic drinking solution greatly decreased early death due to cytoxan toxicity when given either as monotherapy, or when combined with surgical castration. The antibiotic drinking water was prepared by crushing 31 tablets of bactrim DS (160 mg trimethoprim and 800 mg sulfamethoxazole, Roche Labs), in a mortar and pestle. The bactrim powder was placed in approximately 1 liter of a solution composed of 40% propylene glycol/10% ethanol/50% water (v/v/v). This combination was mixed with a stirring rod and then sonicated until all visible grains disappeared. The pH was adjusted to 10 and then the mixture was added to 50 liters of water with stirring. To the final solution, 125 ml of Biosol (Roche Labs), in a mortar and pestle. The bactrim powder was placed to surgery secondary to Cytoxan induce immunosuppression, animals were placed on daily prophylactic antibiotics in the drinking water and given Cytoxan alone or plus surgical castration. These studies demonstrated that the daily antibiotic treatment essentially eliminated early deaths (i.e., within the first 10 days) following Cytoxan treatment when given either by itself or when combined with surgical castration. Thus in all further Cytoxan treatment, prophylactic antibiotics were used.

Statistical Analysis. All group data are presented as the mean ± SE. Statistical analysis of the data was performed by a one-way analysis of variance followed by Duncan’s multiple-range test of the difference between group means.

RESULTS

Determination of Chemotherapy Regimen to be used in Combined Chemo-Hormonal Therapy. Previous studies demonstrated that by combining castration with simultaneous initiation of Cytoxan treatment, survival of H tumor bearing animals could be increased over that produced by either monotherapy alone, but no cures were produced (14). In these earlier studies, Cytoxan was given at a dose of 100 mg/kg body weight once every 21 days for two doses. To cure H tumor-bearing rats with such combined chemo-hormonal therapy, more than two cycles of Cytoxan treatment are thus needed. In addition, decreasing the time between cycles is critical to maximize the possibility of cures. In previous studies, it was found that bladder hemorrhage with varying degrees of hematuria (i.e., hemorrhagic cystitis) and a >80% decrease in the white blood cell (WBC) counts (i.e., immunosuppression) was induced within 4 days after a single i.p. Cytoxan treatment when given at a dose of >50 mg/kg. In addition, if a single i.p. injection of Cytoxan, at a dose >50 mg/kg, was simultaneously initiated at the time of surgical castration, a highly variable frequency of early deaths (i.e., within 7–10 days) due to acute infection was obtained. To prevent early deaths due to either hemorrhagic cystitis (followed by adventitious bacterial cystitis) or adventitious infection due to surgery secondary to Cytoxan induce immunosuppression, animals were placed on daily prophylactic antibiotics in the drinking water and given Cytoxan alone or plus surgical castration. These studies demonstrated that the daily antibiotic treatment essentially eliminated early deaths (i.e., with the first 10 days) following Cytoxan treatment when given either by itself or when combined with surgical castration. Thus in all further Cytoxan treatment, prophylactic antibiotics were used.

Hematological studies demonstrated that the WBC depression induced by i.p. Cytoxan at a dose of >50 mg/kg was limited to approximately 8–10 days. Thus by 14 days following exposure to Cytoxan, the WBC counts returned to normal. Therefore, experiments were performed to test the dose-response toxicity of Cytoxan when given i.p. as multiple doses at 14-day intervals to antibiotic treated Copenhagen male rats. Ten rats per group were treated with either 200, 150, 100, 90, 70, or 50 mg/kg every 14 days. These studies demonstrated that the maximal dose of Cytoxan which could be given for 8 cycles without producing death was 90 mg/kg. If higher dose of Cytoxan were given >50% of animals died before eight doses of drug could be administered. When 90 mg/kg was given for eight cycles, no animals died and there was <15% difference in body weight between Cytoxan treated and age-matched untreated control rats. In addition, there were only minor effects upon food consumption (i.e., <10% reduction in food consumption during first week followed by a return to normal consumption with 14 days). H₂O consumption, however, was still effected by the 90 mg/kg Cytoxan dose with ~40% reduction in H₂O intake within the first 4 days of Cytoxan treatment with a return to normal intake by 12–14 days. At a dose of 90 mg/kg, the WBC count was reduced to 20% of starting number within 4 days of Cytoxan treatment, however, the normal number of WBC was restored by 9–10 days following the 90 mg/kg Cytoxan treatments. While there was no mortality to 90 mg/kg of Cytoxan when given every 14 days for a total of eight cycles in the antibiotic treated animals, if additional cycles at this dose were given, a sharp rise in mortality occurred (i.e., ≥50% of animals died if they received one to two additional doses). Since this effect was also seen for the 70 and 50 mg/kg treatment group, the 90 mg/kg dose of Cytoxan given every 14 days for eight cycles was chosen as standard chemotherapy to be used in the chemo-hormonal therapy studies which followed.

Effect of Tumor Size on the Survival of R-3327 H Tumor-bearing Rats Treated with Hormonal Therapy Alone, Chemotherapy Alone, or with Combined Chemo-Hormonal Therapy. Trocar pieces (~10 mg) of the slow growing, well-differentiated H prostatic adenocarcinoma were implanted s.c. into the flank of 40 Cop rats and allow to go untreated for 150 days. By this time, all inoculated animals developed a 1–2 cm³ size H tumor which was growing with a mean volume doubling time of 20.5 ± 2.5 days. The 40 H tumor-bearing animals were randomized into four groups of 10 tumor bearing rats each. One group received no treatment to serve as an intact control group. The second group was surgically castrated at this 1–2 cm³ starting...
size (i.e., day 150 postinoculation). The third group was similarly starting at day 150 on 90 mg/kg body weight of Cytoxan, given every 14 days for eight total doses. The fourth group was castrated and simultaneously started on Cytoxan treatment (90 mg/kg, once every 14 days for eight doses) also when the tumor was 1-2 cm³ in starting size (i.e., day 150 posttumor inoculation). All animals were followed until death and mean survival for each group calculated, Table 1. These results demonstrated that it took ~1 year for an untreated intact H tumor-bearing rat to succumb to its cancer. Both castration alone or Cytoxan treatment alone of intact hosts increased the mean host survival by over 2 months as compared to untreated intact controls; however, no animal was cured by either of the monotherapies. Combining castration and the simultaneous initiation of Cytoxan treatment increased the mean host survival by 8 additional months as compared to untreated controls, a value >6 months longer than that observed for either treatment when given alone. Again, however, no animal was cured by these combined chemo-hormonal treatment when the therapy was initiated at a time when the starting H tumor size was 1-2 cm³.

Histological examination of the tumors at the time of death revealed well-differentiated adenocarcinomas which were morphologically indistinguishable between the treatment groups. In addition, the morphology of these tumors was indistinguishable from that of starting H tumor used to inoculate each animals initially.

A second similar experiment was performed on H tumor-bearing rats, however, this time therapy (i.e., castration alone, Cytoxan alone, or castration plus Cytoxan) was initiated when the tumor was ≤0.2 cm³ not 1-2 cm³ in starting size. To do this 40 Cop male rats were inoculated with H tumor and then 60 days later, the animals were randomized into the same four groupings as previously described (i.e., intact, castrate alone, Cytoxan alone, castrate plus Cytoxan group). At 60 days, all animals had palpable growing tumors which were ≤0.2 cm³. The animals were followed until death or until 700 days postinoculation, Table 2. Again untreated intact control animal survived ~1 year with the H tumor. Treatment with either castration alone or Cytoxan alone, when initiated when the tumor is ≤0.2 cm³ increased host survival by 4-5 months as compared to untreated intact control animals. This increase was longer (i.e., ~2 months longer) than that produced by the respective monotherapies if each was initiated when the H tumor is ≤0.2 cm³, not 1-2 cm³ in starting size (compare Tables 1 and 2). As in the previous experiment, combination of castration and simultaneous initiation of Cytoxan treatment produced an increase in mean survival (i.e., >9 months) over that produced by either monotherapy alone. In contrast to the previous experiment, however, such combined chemo-hormonal treatment resulted in 40% of treated animals being cured (i.e., no evidence of palpable tumors >700 days postinoculation and no indication of any residual cancer cells histologically at autopsy). Thus, the same combined chemohormonal therapy which was not curative when initiated when the H tumor was 1-2 cm³ in starting size (Table 1) was curative in a proportion of animals when initiated at a smaller H tumor burden (i.e., ≤0.2 cm³ in size).

Again, histological evaluation of the tumors harvested at autopsy from animals not cured revealed well-differentiated adenocarcinoma which were morphologically indistinguishable between the various treatment groups.

Effect of Tumor Size on the Survival of R-3327 G Tumor-bearing Rats Treated with Hormonal Therapy Alone, Chemotherapy Alone, or with Combined Chemo-Hormonal Therapy. Trocar pieces (~10 mg) of the fast growing, poorly differentiated G prostatic adenocarcinoma were implanted s.c. into the flank of 40 Cop rats and allowed to go untreated for 1 month. By this time, all inoculated animals developed a 1-2 cm³ size G tumor which was growing with a mean volume doubling time of 4.1 ± 0.2 days. The 40 G tumor-bearing animals were randomized into four groups of 10 tumor-bearing rats each. One group received no treatment to serve as an intact control group. The second group was surgically castrated at this 1-2 cm³ starting size. The third group was similarly starting on 90 mg/kg body weight of Cytoxan given every 14 days for eight total doses when the G tumors were 1-2 cm³ in size. The fourth group was castrated and simultaneously started on Cytoxan treatment (90 mg/kg, once every 14 days for eight doses) also when the tumor was 1-2 cm³ in starting size. All animals were followed until death and mean survival for each group calculated, Table 3. These results demonstrated that it took ~3 months for an untreated intact G tumor-bearing rat to succumb to its cancer. Castration alone increased the mean host survival by over 2.5 months, while Cytoxan treatment of intact hosts increased the mean host survival by 3.5 months, as compared to untreated intact controls. No animal was cured by either of the monotherapies alone. Combining castration and the simultaneous initiation of Cytoxan treatment, however, increased the mean host survival by ~6 additional months as compared to untreated controls, a value >2.5 months longer than that observed for either treatment when given alone. Again, however,

Table 1 Effect of various treatments on the survival of R-3327 H tumor-bearing rats initiated when the tumor is 1-2 cm³ in starting size

<table>
<thead>
<tr>
<th>Treatment of H tumor-bearing rats</th>
<th>Average host survival (days posttumor inoculation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None; intact control</td>
<td>360 ± 15</td>
</tr>
<tr>
<td>Castrated 150 days after inoculation when the tumor is 1-2 cm³</td>
<td>428 ± 12</td>
</tr>
<tr>
<td>Intact given Cytoxan starting 150 days after inoculation when tumor is 1-2 cm³</td>
<td>432 ± 10</td>
</tr>
<tr>
<td>Castrated and given Cytoxan starting 150 days after inoculation when the tumor is 1-2 cm³</td>
<td>600 ± 34</td>
</tr>
</tbody>
</table>

* Ten tumor-bearing rats per group.
* Cytoxan treatment = 90 mg/kg every 14 days for eight total doses.
* P < 0.01 compared to either castrate alone or Cytoxan alone groups.

Table 2 Effect of various treatments on the survival of R-3327 H tumor-bearing rats initiated when the tumor is ≤0.2 cm³ in starting size

<table>
<thead>
<tr>
<th>Treatment of H tumor-bearing rats</th>
<th>Average host survival (days posttumor inoculation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None; intact control</td>
<td>340 ± 21</td>
</tr>
<tr>
<td>Castrated 60 days after inoculation when the tumor is ≤0.2 cm³</td>
<td>490 ± 15</td>
</tr>
<tr>
<td>Intact given Cytoxan starting 60 days after inoculation when the tumor is ≤0.2 cm³</td>
<td>455 ± 20</td>
</tr>
<tr>
<td>Castrated and given Cytoxan starting 60 days after inoculation when the tumor is ≤0.2 cm³</td>
<td>680 ± 29* (60%)</td>
</tr>
</tbody>
</table>

* Ten tumor-bearing rats per group.
* Cytoxan treatment = 90 mg/kg every 14 days for eight total doses.
* P < 0.01 compared to untreated intact control.

Table 3 Effect of various treatments on the survival of R-3327 G tumor-bearing rats initiated when the tumor is 1-2 cm³ in starting size

<table>
<thead>
<tr>
<th>Treatment of G tumor-bearing rats</th>
<th>Average host survival (days posttumor inoculation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None; intact controls</td>
<td>100 ± 28</td>
</tr>
<tr>
<td>Castrated at 1 month after inoculation when the tumor is 1-2 cm³</td>
<td>176 ± 12</td>
</tr>
<tr>
<td>Intact given Cytoxan starting 1 month after inoculation when the tumor is 1-2 cm³</td>
<td>215 ± 7*</td>
</tr>
<tr>
<td>Castrated and given Cytoxan starting 1 month after inoculation when the tumor is 1-2 cm³</td>
<td>279 ± 23*</td>
</tr>
</tbody>
</table>

* Ten tumor-bearing rats per group.
* Cytoxan treatment = 90 mg/kg every 14 days for eight total doses.
* P < 0.01 compared to untreated intact control.
* P < 0.01 compared to either castrate alone or Cytoxan alone groups.

NED, no evidence of disease.
no animal was cured by combined chemo-hormonal treatment when the therapy was initiated at a time when the starting G tumor size was 1–2 cm³.

Histological examination of the tumors at the time of death revealed poorly differentiated adenocarcinomas which were morphologically indistinguishable between the various treatment groups. In addition, the morphology of these tumors were indistinguishable from that of the starting G-tumor used to inoculate each animal initially.

A second similar experiment was performed on G tumor-bearing rats, however, this time therapy (i.e., castration alone, Cytoxan alone, or castration plus Cytoxan) was initiated when the tumor was ≤0.2 cm² not 1–2 cm² in size. To do this 40 Cop male rats were inoculated with G tumor and then 10 days later, the animals were randomized into the same four groupings as previously described (i.e., intact, castrate alone, Cytoxan alone, castrate plus Cytoxan group). By 10 days, all animals had palpable growing tumors which were ≤0.2 cm². The animals were followed until death or until 700 days postinoculation.

Table 4. Again untreated intact control animals survived ~3 months with the G tumor. Castration of the host when the tumor is ≤0.2 cm² increased the mean survival by ~3.5 months as compared to untreated intact control animals. Survival for intact G tumor-bearing rats given only Cytoxan when the tumors were ≤0.2 cm² was increased by more than 6 months. These increases in survival were longer (i.e., ~ additional 1.5 months for castration and additional 2.8 months for Cytoxan) than that produced by the respective monotherapies if each was initiated when the G tumor is ≤ 0.2 cm², not 1–2 cm² in starting size (compare Tables 3 and 4). As in the previous G tumor experiment, combination of castration and simultaneous initiation of Cytoxan treatment produced an increase in mean survival (i.e., >10 months) over that produced by either monotherapy alone. In contrast to the previous G tumor experiment, however, such combined chemo-hormonal treatment resulted in 30% of treated animals being cured (i.e., no evidence of palpable tumor >700 days postinoculation and no indication of any residual cancer cells histologically at autopsy). Thus, the same combined chemo-hormonal therapy which was not curative when initiated when the G tumor was 1–2 cm³ in starting size (Table 3) was curative in a proportion of animals when initiated at a smaller G tumor burden (i.e., ≤0.2 cm² in size).

Again, histological evaluation of the tumors harvested at autopsy from animals not cured revealed poorly differentiated adenocarcinomas which were morphologically indistinguishable between the various treatment groups.

**DISCUSSION**

Prostatic cancers are rarely homogeneous with regard to the clones of cancer cells comprising individual tumors by the time they became clinically manifest in humans. For example, Kastendieck (17) demonstrated that of 180 clinically manifest prostatic cancers removed surgically from previously hormonally untreated patients, 60% of these cancers were already histologically heterogeneous being composed of a mixture of several different cancer cell types of widely varying differentiation (admixture of glandular, cribriform, and anaplastic morphology within the same cancer). These results demonstrate that prostatic cancer cell heterogeneity can occur early in the clinical course of the disease and there is no requirement for androgen ablation to induce this morphological heterogeneity. This last point is also demonstrated by the study of Viola et al. (18) in which immunoperoxidase staining methods were used to examine the cellular distribution of prostate-specific antigen, carcinoembryonic antigen, and p21 Harvey-ras oncogene protein within individual prostatic cancers from patients with metastatic disease and who had received no prior hormonal therapy. This study again demonstrates that each of these phenotypic parameters is heterogeneously distributed, with multiple foci of both nonreactive and reactive cancer cells present within individual prostatic cancers.

Based upon these morphological and immunocytochemical studies, it is clear that individual human prostatic cancers are heterogeneously composed of clones of phenotypically distinct prostatic cancer cells even before hormonal therapy is begun. This has led a series of investigators (6–9) to suggest that the major reason androgen withdrawal therapy is not curative, is not due to an inadequate decrease in the systemic level of androgen following therapy, but is instead due to the fact that prostatic cancers are heterogeneously composed of clones of both androgen-dependent and -independent cancer cells even before hormonal therapy is begun. Treatment of such a heterogeneous prostatic cancer with androgen withdrawal alone kills only the androgen-dependent clones of cancer cells present without eliminating the preexisting androgen-independent prostatic cancer cells, no matter how complete this androgen withdrawal therapy might be. To effect all of the heterogeneous prostatic cancer cell populations within an individual patient, effective chemotherapy specifically targeted against the preexisting androgen independent cancer cell must be combined with androgen ablation targeted at the androgen-dependent cancer cells.

In the present animal studies, the validity of this point is clearly demonstrated. These data demonstrate that the survival of animals bearing either the slow growing, well-differentiated H or the fast growing, poorly differentiated G Dunning prostatic cancer is greater when a combined chemo-hormonal therapy is used than when either monotherapy is used alone. In order for such a combined chemo-hormonal therapy to be superior to hormonal therapy alone, however, the chemotherapy agent used must be effective against the prostatic cancer cells when used as monotherapy. Cytoxan, as used in the present studies (i.e., 90 mg/kg given every 14 days for eight cycles), demonstrated such effectiveness when used alone against both the H and G rat prostatic cancers. Similarly, both the transplantable Noble (19) and Lobund PA rat prostatic cancers (20) have been demonstrated to be responsive to Cytoxan. In contrast to the situation in these rodent studies, Cytoxan has not, however, been reported to be very useful in the treatment of human prostatic cancers (2). Chemothapeutic agents which demonstrate a high degree of effectiveness when used against rodent adenocarcinomas are often not as effective when used to treat human solid cancers (21). The reason for this difference is usually ascribed to the fact that animal cancers have a higher growth fraction and are thus more sensitive to antiproliferative...
chemotherapy than their human counterparts (22, 23). In the rodent models, the chemotherapies which have been demonstrated to be curative nearly universally are so only if they are initiated at a time when the total tumor burden is low (24, 25). If the chemotherapy is not used against a low tumor burden the effectiveness is greatly reduced, even in animals. In contrast, chemotherapy used against human prostatic cancer is usually initiated late in the course of the disease when the tumor burden is large. Such an approach to late chemotherapy has had only limited success against human prostatic cancer (2, 26).

In the present animal studies, like the human situation, it was demonstrated that when chemotherapy (Cytoxan) is given by itself to animal bearing large H or G tumor (i.e., 1-2 cm$^3$ size tumor), it is less effective than when initiated when the H or G tumor burden is small (i.e., $\leq 0.2$ cm$^3$ size tumor). In addition, cures of a proportion of the H or G tumor bearing animals were only achievable by a combined chemo-hormonal therapy, and even then only if initiated at a small H or G tumor burden (i.e., $\leq 0.2$ cm$^3$ size tumor). There results clearly demonstrate that there is an inverse relationship between overall tumor burden and host curability by such chemo-hormonal therapy. These studies suggest that the ineffectiveness of a drug (e.g., Cytoxan) when used against large prostatic tumor burden may not predict the effectiveness of the drug on small tumor burden, for example, upon microscopic metastatic prostatic cancer deposit throughout the body. Therefore, it may be premature to believe that all chemotherapeutic agents which have been demonstrated to be ineffective in the treatment of human prostatic cancer when tested against large metastatic tumor burden might not be more effective when used in combination with hormonal therapy early in the clinical course of the disease.

This point is particularly relevant to the recent advances in the urological management of patients with a palpable tumor believed to be confined to the prostate (i.e., clinical stage B patients). Such patients are not only candidates for radical prostatectomy, but with the development of the nerve sparing modification (27) larger numbers of such men than ever before are undergoing this modified radical prostatectomy. It is well established, however, that approximately 50% of these clinical state B patients will not be cured of their disease (28) (50% of these patients actually have microscopically established metastatic cancer at the time of surgery). Since at least 50% of clinical stage B patients, will already have microscopic metastatic disease at the time of surgery, randomized clinical trials comparing surgery alone versus surgery plus adjuvant chemo-hormonal therapy could be initiated on these stage B prostatic cancer patients. In such trials, the hormonal arm of the chemo-hormonal therapy could utilize LHRH (2) analogues, instead of surgical orchietomy. Since the chemical orchietomy that LHRH analogues produces is reversible, and toxicity to these agents is not great, LHRH analogue + Cytoxan treatment could be initiated immediately following radical prostatectomy to patients with stage B prostatic cancer and continued for a limited period (6 months to 1 year) to test if this adjuvant chemo-hormonal therapy could increase the cure rates.

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REFERENCES

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