

Adaptive Therapy for Androgen-Independent Prostate Cancer: A Randomized Selection Trial of Four Regimens

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- Background** Physicians typically switch therapies unless clinically relevant thresholds of response are observed, and treatments that produce high-quality responses and that are active in the salvage setting are generally felt to be promising. With the goal of efficiently selecting promising regimens for more advanced trials, we conducted a randomized selection trial of four regimens to identify promising treatments for androgen-independent prostate cancer.
- Methods** Patients without prior exposure to cytotoxic therapy were randomly assigned to one of four regimens (i.e., cyclophosphamide, vincristine, and dexamethasone [CVD]; ketoconazole plus doxorubicin alternating with vinblastine plus estramustine [KA/VE]; weekly paclitaxel, estramustine, and carboplatin [TEC]; paclitaxel, estramustine, and etoposide [TEE]). Patients were evaluated every 8 weeks to assess response and adverse events. Patients who responded continued with the same treatment; those who did not were randomly assigned to one of the other three treatments. Response was assessed by considering tumor-specific symptoms, tumor regression, and prostate-specific antigen (PSA) changes. Treatment was continued until two consecutive courses induced a response (i.e., overall success, the major criterion for which was 80% PSA reduction) or until patients were given two different regimens that failed to induce such a response.
- Results** Median overall survival from registration among all 150 patients was 22 months (95% confidence interval [CI] = 19 to 26 months). Estimated survival at 3 and 5 years, respectively, was 26% (95% CI = 20% to 35%) and 10% (95% CI = 5% to 16%). Overall success was achieved in 35 patients with the initial treatment (i.e., four treated with CVD, seven with KA/VE, 14 with TEC, and 10 with TEE) and in nine more patients with a second-line regimen (i.e., two with CVD, five with KA/VE, and two with TEC). For all 44 (29%, 95% CI = 23% to 37%) patients with overall success, median survival was 30 months (95% CI = 26 to 40 months); for the other 106 patients, it was 19 months (95% CI = 17 to 22 months). TEC produced the greatest number and proportion of successful courses of treatment, and TEC followed by KA/VE was the most promising two-stage strategy.
- Conclusions** Some patients responded to particular treatments, and responses to second-line treatments were not rare. We propose that TEC be considered for phase III evaluation.

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Prostate cancer occurs predominantly in older men and has a remarkably long natural history. Even so, most patients with clinically apparent metastatic prostate cancer who require treatment with androgen ablation will develop androgen-independent disease before succumbing to comorbid conditions. Clinical disease progression despite androgen deprivation is the cause of death in approximately 90% of patients in whom it develops. Because approximately 40 000 men in the United States develop clinically apparent metastases from prostate cancer each year, there is a pressing and unmet need for effective systemic therapy.

Although growth of prostate cancer in a hypogonadal state is not independent of the hormonal milieu or of the signaling competence of the androgen receptor, prostate cancers that grow in low levels of serum testosterone (usually defined as less than

50 ng/dL) are usually described as androgen independent or castration resistant. Use of cytotoxic chemotherapy for patients with androgen-independent prostate cancer has been, and largely

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CONTEXT AND CAVEATS

Prior knowledge

Defined methods to select promising therapeutic agents for advanced trials (such as phase III randomized trials) are lacking.

Study design

An algorithm was designed for a randomized selection trial to identify promising treatments for androgen-independent prostate cancer for more advanced trials. Four different chemotherapy regimens were studied, taking account of both first-line and second-line treatments.

Contribution

Some patients responded to particular treatments, and responses to second-line treatments were not rare. The regimen of weekly paclitaxel, estramustine, and carboplatin (TEC) produced the greatest number and proportion of successful courses of treatment, and TEC followed by a regimen of ketoconazole plus doxorubicin alternating with vinblastine plus estramustine was the most promising two-stage strategy.

Implications

The algorithm and analysis used in this study appear to be a useful method for the selection of promising therapies.

Limitations

This is a single-institutional study among a population of prostate cancer patients that is more highly motivated and resourceful than the general population of such patients. Validation of this method in independent populations of patients is required.

remains, unsatisfactory in terms of improving survival, although a palliative benefit from chemotherapy has long been recognized (1). Definitive demonstration of a modest alteration in the natural history of androgen-independent prostate cancer has only recently been obtained by use of docetaxel (2,3).

In 1998, when this trial was conceived, there were several regimens with palliative utility in use at M. D. Anderson Cancer Centre. We turned our attention to the problem of selecting one or more treatments for more advanced clinical trials. From an informal assessment of our clinical experience, we identified four regimens of interest. Because oncologists typically offer patients sequential treatments if clinical success is not achieved with the first-line treatment and because success with a second-line treatment is usually taken to be a harbinger of promising biologic activity, we sought a clinical trial design that would take account of these familiar clinical elements.

These considerations led us to design a clinical trial for patients with androgen-independent prostate cancer that included four different regimens, all from an era when docetaxel was not available. If first-line and second-line treatments are drawn from a pool of four regimens, then there are 12 different two-stage sequences of one treatment followed by another if the first fails to produce the desired response. This design is a "play the winner, drop the loser" strategy for assigning treatments to a patient over multiple courses of therapy. Such a strategy, which is familiar and intuitive to clinicians, seeks the most active treatment for a given patient. Before conducting the trial, we established a statistical analytic framework, taking into account the first- and second-line treatments, as

well as possible interactions between them. An extensive computer simulation was carried out to establish the design's operating characteristics (4). This methodologic research confirmed that such a trial would be statistically powerful for various treatment selection goals in clinically relevant scenarios used in the simulation studies. In this article, we report the final results of the first clinical trial, to our knowledge, to apply our formal analytic framework to this familiar clinical treatment allocation paradigm.

Patients and Methods

Patients

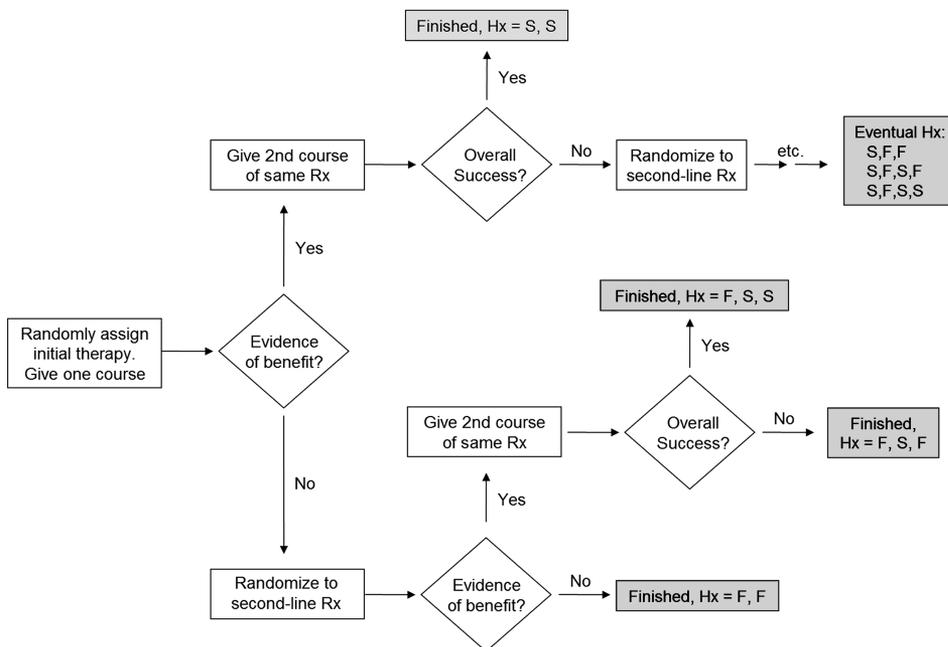
This was a single-institution trial, with all patients accrued from the Genitourinary Medical Oncology Department at The University of Texas M. D. Anderson Cancer Center. The trial was opened December 8, 1998, and was closed to accrual January 29, 2003; follow-up was completed December 31, 2006. Eligible patients had progressive prostate cancer despite adequate testosterone suppression, which was stringently defined as a serum testosterone level of less than 30 ng/dL, and withdrawal (if applicable) of androgen receptor antagonists. Only patients with adenocarcinoma of apparently acinar origin were eligible. No previous exposure to cytotoxic therapy was allowed, but patients treated with any sort of hormonal therapy were eligible. All patients had adequate physiologic reserve as indicated by a Zubrod performance status (5) of 2 or less, a transaminase level of less than twice the upper limit of normal, a creatinine clearance of at least 35 mL/min, a platelet count of at least 120 000 platelets per μ L, and a hemoglobin level of at least 10.5 g/dL without transfusion support. In addition, patients had to have either no history of cardiac disease or a measured left ventricular ejection fraction of at least 45%.

Patients were excluded if they were on supraphysiologic doses of corticosteroids (defined as >7.5 mg of prednisone equivalents per day), had a requirement for gastric acid suppression (or were achlorhydric from any cause), or were taking medications that were known to have potentially adverse interactions with ketoconazole (such as terfenadine, omeprazole, cisapride, or astemizole) because these patients would not be candidates for treatment with the regimen that contained ketoconazole (i.e., ketoconazole plus doxorubicin alternating with vinblastine plus estramustine [KA/VE]).

Patients were prospectively stratified by disease burden as high and low volume, and these categories were used to balance the initial randomization. Patients were classified as high volume if they had more than three areas of presumed pathologic uptake on bone scan, involvement of the appendicular skeleton, or visceral involvement. Patients were classified as low volume if they had none of these features. In addition, for the purpose of prognostic modeling, patients were classified into five prospectively defined categories that were based on the extent of disease: local involvement only; lymph node involvement (i.e., any lymph node involvement at any site); low-volume bone involvement (i.e., three sites or less on a bone scan); high-volume bone involvement (i.e., more than three sites on a bone scan); and visceral or soft-tissue involvement. These categories were included in a multivariable model of outcome as described below.

All patients provided written informed consent for this study, which was approved by The University of Texas M. D. Anderson

Fig. 1. Treatment assignment algorithm. All possible outcome histories for all response endpoints are shown (for the numbers of patients treated with each regimen and at each outcome history, see Table 3). Rx = treatment; Hx = outcome history to that point in trial; F = failure; S = success.



Cancer Center Institutional Review Board. Because all regimens investigated were considered to be well established, study treatment could be administered by local oncologists with patients returning to The University of Texas M. D. Anderson Cancer Center every 8 weeks for clinical evaluation and treatment assignment for the next course.

Multicourse Treatment Assignment Algorithm

At enrollment, patients were randomly assigned to an 8-week course of treatment with one of the four regimens being examined, with subsequent courses assigned on the basis of outcome (Fig. 1). Each patient's clinical outcome for each course of therapy was scored as a success (S) or failure (F), according to the criteria elaborated below. The primary outcome data from the trial thus consisted of a treatment identifier and an outcome indicator (i.e., S or F) for each course for each patient. The four regimens included were as follows: cyclophosphamide, vincristine, and dexamethasone (CVD); KA/VE (6); weekly paclitaxel, estramustine, and carboplatin (TEC) (7); and paclitaxel, estramustine, and etoposide (TEE) (8). The details of dose and schedule for these four regimens are summarized in Table 1.

Treatment assignments in courses after the first were done according to the following algorithm (Fig. 1). After an initial 8-week course of therapy, patients were evaluated. To continue with the same treatment, patients had to have evidence of a benefit (i.e., criteria for scoring that course of treatment as a success), which we defined as follows: a prostate-specific antigen (PSA) decline of at least 40% from baseline; objective regression (of any magnitude) of any measurable (i.e., assessable in two dimensions) disease; improvement in any cancer-related symptoms (principally pain or constitutional symptoms, such as anorexia, asthenia, or cachexia); and no new lesions or new cancer-related symptoms. Criteria for scoring a second course of the same treatment as a success (i.e., an overall success, so that no second regimen would be needed) were more stringent: a PSA decline of at least 80%

from baseline; resolution of all cancer-related symptoms; an objective tumor regression of at least 50% (as represented by the product of the longest tumor diameter and its perpendicular diameter) from baseline for all measurable lesions; and no new lesions or cancer-related symptoms. The PSA criteria required not only the relative reductions noted but also no subsequent increase in the PSA level, even if the PSA remained below the 40% or 80%

Table 1. Dose and treatment schedule for all agents in each regimen evaluated in this trial*

Regimen, interval between treatments	Ref.	Agents and schedule
CVD, 4 wk		Cyclophosphamide, 250 mg, orally for 14 days Vincristine, 1 mg, IV, days 1, 8, and 15 Dexamethasone, 0.75 mg, days 1–14
KA/VE, 8 wk	(6)	Ketoconazole, 400 mg, orally, tid, weeks 1, 3, and 5 Doxorubicin, 20 mg/m ² , IV, days 1, 15, and 29 Vinblastine, 3 mg/m ² , IV, days 8, 22, and 36 Estramustine, 140 mg, orally, tid, weeks 2, 4, and 6
TEC, 8 wk	(7)	Hydrocortisone, 10 mg, orally, bid, daily Taxol, 80 mg/m ² , weekly for 6 wk Estramustine, 280 mg, orally, tid, 5 days/wk, weeks 1–6 Carboplatin, AUC of 2 mg/mL per min, weekly for 6 wk
TEE, 3 wk	(8)	Taxol, 135 mg/m ² , day 2 Estramustine, 280 mg, orally, tid, days 1–14 Etoposide, 50 mg, orally, bid, days 1–14

* CVD = cyclophosphamide, vincristine, and dexamethasone; IV = intravenously; KA/VE = ketoconazole plus doxorubicin alternating with vinblastine plus estramustine, estramustine; tid = three times per day; bid = two times per day; TEC = weekly paclitaxel, estramustine, and carboplatin; AUC = dosing basis for carboplatin expressed as the target area under the curve for clearance of carboplatin; TEE = paclitaxel, estramustine, and etoposide.

threshold at the end of the course. At the first course that was judged a failure (so that the outcome history to that point was either F or SF), the patient was randomly assigned to one of the other three treatment regimens in this trial. The same criteria were used to evaluate outcomes after one or two courses of the second-line therapy. Any second failure (i.e., with an outcome history of FF, FSF, SFF, or SFSF) met the primary endpoint of the trial. Patients achieving overall success (i.e., those with an outcome history of SS, FSS, or SFSS) also met the primary endpoint of the trial. In summary, overall success with a particular treatment was defined as two consecutive successful courses; overall treatment failure was defined as any two unsuccessful courses, regardless of treatment. With four regimens under consideration, these treatment assignment rules define 76 possible treatment and outcome histories for an individual patient.

Although this treatment allocation is equivalent to a multiarm randomization among all 12 possible two-stage strategies, it is more intuitive to think of it as shown in Fig. 1, with rerandomization if the first-line treatment fails to produce SS in the first two courses. Rerandomization could also allow rebalancing for dominant prognostic factors (although rebalancing was not done in this trial).

This multicourse treatment assignment algorithm is a particular case of what is more generally a two-stage outcome-adaptive treatment strategy (A,B) that consists of giving treatment A until either overall success or failure is declared and then switching to treatment B if failure with treatment A is observed. For our case, subscribing each per-course outcome (S or F) with the treatment given in that course (A or B), the seven possible outcomes with strategy (A,B) are $\{S_A S_A\}$ (i.e., overall success with treatment A initially), $\{F_A S_B S_B\}$ or $\{S_A F_A S_B S_B\}$ (i.e., overall success with treatment B after a failure with treatment A), or $\{F_A F_B, F_A S_B F_B, S_A F_A F_B, S_A F_A S_B F_B\}$ (i.e., overall failure). Thus, each patient could receive two, three, or four courses of treatment. Because there are four regimens under consideration, there are a total of 12 strategies. Because treatment B can only be given after a course in which treatment A failed to achieve overall success, the outcomes $S_A S_B$ and $S_A F_B$ cannot occur.

Some familiar and clinically intuitive notions were embedded in this treatment assignment algorithm. The notion of evidence of benefit at 8 weeks corresponds to what is more conventionally termed a response. After an initial response, continued response to a treatment can produce what we have termed an overall success (as defined above). This response corresponds to what is commonly regarded as high response quality. Response quality is seldom defined precisely, but a high-quality response is generally understood to have sufficient magnitude and duration to be of unequivocal benefit to the patient (such as a “complete response”). Finally, success after some other treatment has failed is commonly known as non-cross-resistance, i.e., a previous failure of treatment A does not adversely prejudice the probability of benefit from subsequent application of treatment B.

Statistical Model

Guided by these clinically grounded notions, we constructed a conditional logistic regression model for the probability of response in each course, given the patient’s previous treatment and outcome history. The model may be expressed as follows. Let t denote treat-

ment; $j = 1, 2, 3,$ or 4 denote the course; and $Y_j = 1$, if success occurred in course j , or $Y_j = 0$, if failure occurred. To account for the patient’s history before course j , we defined the variable $Z_j = 0$ for histories of untreated or S, $Z_j = 2/3$ for histories of F or FS, and $Z_j = 2/5$ for histories of SF or SFS. These particular numerical values were obtained from a general model (4) for Z_j as a smoothed average number of failures through the most recent course that was a failure, to quantify the unfavorable influence of the patient’s history relative to being untreated. (These values are somewhat arbitrary, but the conclusions of the model are insensitive to the exact values anyway.) Let $p_{t,j} = \text{Pr}(S \text{ in course } j \mid \text{current treatment } t \text{ and previous history})$ —i.e., the conditional probability of success with treatment t in course j , given the patient’s previous history. With these definitions, a logistic regression model was defined as follows:

$$\ln[p_{t,j}/(1 - p_{t,j})] = m_t + a_t Y_{t,j-1} + b_t Z_{t,j-1} + cI(\text{low disease volume}).$$

The response probability in any given course is defined conditionally given the patient’s history of treatment and outcomes, and the unit of observation is a patient course. In this model, parameter m_t represents the first-line response rate, and it corresponds directly with probability of success in course 1. Parameter a_t represents the response quality and applies only after a previous course with the same treatment that was judged successful; i.e., if $Y_{t,j-1} = 1$. Parameter b_t represents cross-resistance, and it applies only in courses that follow some prior treatment failure. Moreover, b_t is weighted by Z , which quantitates the unfavorable influence of previous treatment failure. Parameter c accounts for low (versus high) disease volume at baseline, which is a potentially dominant covariate. This is multiplied by the indicator (I) for low-volume disease ($I = 1$) or high-volume disease ($I = 0$).

Statistical Methods

Unadjusted overall survival probabilities were estimated by the Kaplan–Meier method. Unadjusted between-group comparisons of overall survival were made with the log-rank test (9). Confidence intervals (CIs) for binomial data were calculated by the method of Ghosh (10). The Cox proportional hazards regression model (11) was used to assess the ability of patient characteristics and treatment strategy parameters to predict overall survival, with goodness-of-fit assessed by the Grambsch–Therneau test (12) and martingale residual plots. All computations were carried out in Splus (13). All statistical tests of significance were two-sided.

Results

In the 50-month period between December 8, 1998, and January 29, 2003, 155 patients were registered to participate in this trial. One patient was immediately found to be ineligible and directed toward a more appropriate therapy, and four patients immediately withdrew consent before any treatment. These five patients were excluded from this analysis, but the 150 patients who received any treatment are included, irrespective of subsequent events. Accrual of eligible patients in each of the 4 years the trial was open was 41, 28, 38, and 43 patients per year, respectively.

No statistically significant imbalances were found for baseline characteristics of any covariate for the 150 patients in the analysis (Table 2). Of note, the patients in this study may have had

Table 2. Baseline characteristics of all patients included in this analysis*

Characteristic	Initial regimen received†				Total
	CVD	KA/VE	TEC	TEE	
No. of patients	37	36	38	39	150
Age at registration, No. of patients					
<50 y	1	1	1	1	4
50–70 y	24	20	27	29	100
>70 y	12	15	10	9	46
Prior definitive local therapy, No. of patients					
Radical prostatectomy	8	12	15	14	49
Radiotherapy	14	8	9	7	38
Cryotherapy	0	1	1	0	2
None	15	15	13	18	61
Time from androgen ablation to registration, No. of patients					
<18 mo	14	7	10	18	49
18–48 mo	9	11	10	10	40
>48 mo	14	18	18	11	61
Measurable disease‡, No. of patients					
Yes	11	13	14	10	48
No	26	23	24	29	102
Hemoglobin, No. of patients					
<12.5 g/dL	13	13	14	16	56
≥12.5 g/dL	24	23	24	23	94
Alkaline phosphatase, No. of patients					
≤125 IU/dL	15	20	21	21	77
>125 IU/dL	22	16	17	18	73

* CVD = cyclophosphamide, vincristine, and dexamethasone; KA/VE = ketoconazole plus doxorubicin alternating with vinblastine plus estramustine; TEC = weekly paclitaxel, estramustine, and carboplatin; TEE = paclitaxel, estramustine, and etoposide.

† As first-line treatment.

‡ Presence of lesions that by physical exam or diagnostic imaging could be defined in two dimensions. Bone lesions were not considered to be measurable.

somewhat more advanced prostate cancer than patients currently being considered for the initiation of cytotoxic therapy. For example, among the 150 patients in the analysis, 64 (43%) had nonlocalized disease at their first diagnosis of prostate cancer and, thus, did not receive definitive local therapy. In addition, 96 patients (64%) had either high-volume bone disease (defined as at least three lesions) or visceral metastases at study entry, which was more than expected when the trial was designed.

Prior hormone therapy included luteinizing-hormone releasing hormone agonist only in 78 patients, luteinizing-hormone releasing hormone agonist with an antiandrogen agent in 48 patients, bilateral orchiectomy in 22 patients, conjugated oral estrogens in one patient, and diethylstilbestrol in one patient. Median time from androgen ablation to registration was 35 months (range = 5 to 177 months).

Clinical Outcome

As of December 31, 2006, all patients had experienced disease progression, and 137 (91%) of the 150 patients had died. Median follow-up for survival was 66 months (95% CI = 60 to >74 months). Only one death was not a consequence of prostate cancer—a 71-year-old patient who died of preexisting polycystic kidney disease.

A total of 330 courses of therapy were administered. Patient outcomes in terms of our defined response thresholds for success (tabulated for each response history up to that course) were determined (Table 3). The two prior outcome histories that apply to first-line therapy are untreated (i.e., the initial course) and S, and the four prior outcome histories preceding second-line treatment are F and SF (for the first course of second-line therapy) and FS and SFS (for the second course of second-line therapy). Treatments that failed frequently were selected against—among the 180 treatment assignments that were made adaptively by accounting for the patient's previous history (i.e., treatment in course 2 or later), TEC was given in 58 (33%) of such courses and CVD was given in only 27 (15%) (Table 3).

Table 3. Per-course outcome for patients in this trial*

Regimen	First-line therapy			Second-line therapy			Totals by regimen (%; 95% CI)
	Untreated†	S‡	F§	SF	FS	SFS	
CVD	10/37	4/10	1/8	1/8	1/1	1/1	18/65 (28; 18 to 40)
KA/VE	25/36	7/24	8/17	0/1	5/8	0/0	45/86 (52; 42 to 63)
TEC	26/38	14/25	6/10	7/11	1/5	1/7	55/96 (57; 47 to 67)
TEE	23/39	10/21	2/12	2/8	0/1	0/2	37/83 (45; 34 to 55)
Totals	84/150	35/80	17/47	10/28	7/15	2/10	155/330
% Success	56	44	36	36	47	20	47

* The primary outcome data from the trial are reported as the number of patients who responded to treatment divided by the number of patients assigned that treatment. The table is arranged by current treatment and prior outcome history. S = treatment success; F = treatment failure; CI = confidence interval; CVD = cyclophosphamide, vincristine, and dexamethasone; KA/VE = ketoconazole plus doxorubicin alternating with vinblastine plus estramustine; TEC = weekly paclitaxel, estramustine, and carboplatin; TEE = paclitaxel, estramustine, and etoposide.

† "Untreated" is the outcome history for all patients at the start of treatment, i.e., course 1. For example, there were 38 patients initially assigned TEC, and 26 met our threshold for success in that course.

‡ S is the outcome history for all patients who are beginning course 2 of treatment after a successful outcome in course 1. For example, 10 of the 38 patients initially randomly assigned to CVD had initial success (column 1) and then four of those 10 had success in course 2 (column 2), thus achieving overall success by means of the initially assigned treatment.

§ F is the outcome history for patients for whom the initially assigned treatment failed to meet the threshold for success in course 1. For example, for the KA/VE regimen in this column, 17 patients were scored as F in course 1 (treated in course 1 with CVD, TEC, or TEE) and were subsequently randomly assigned to KA/VE for second-line treatment. As shown, eight of these 17 had success with KA/VE in course 2.

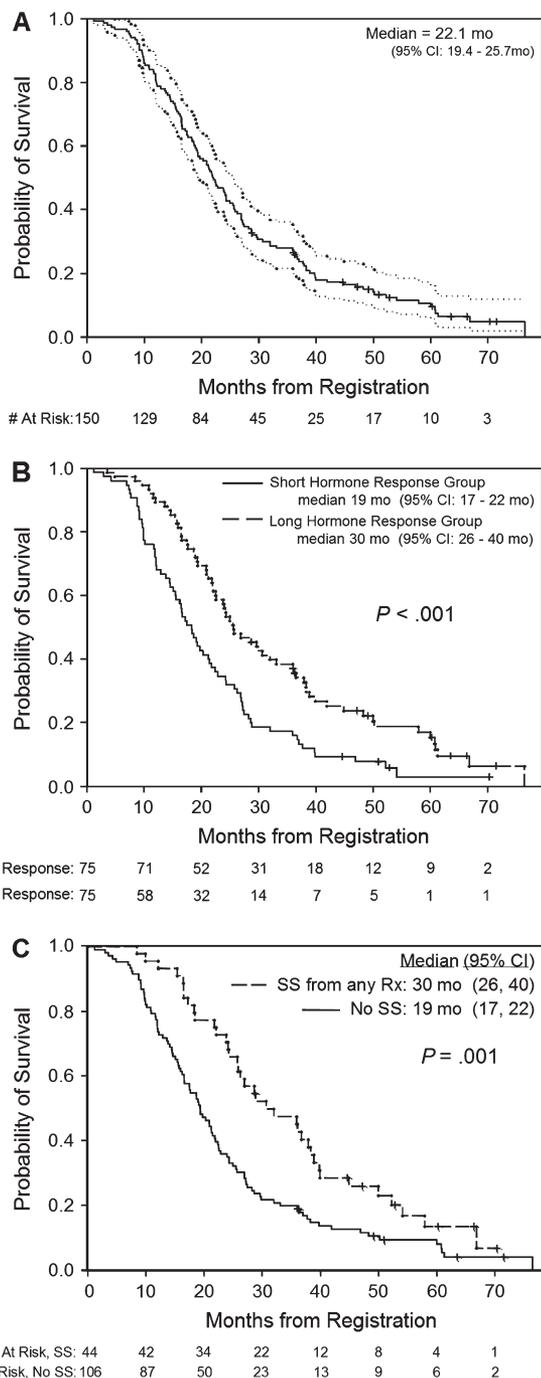


Fig. 2. Survival outcome. **A)** Overall survival of all 150 patients in the analysis, with 95% confidence band (dotted lines). **B)** Overall survival stratified by time from androgen deprivation to registration. Dashed curve = patients with duration of response to hormone therapy of 35 months or more ($n = 75$); solid curve = those with hormone response of less than 35 months ($n = 75$). **C)** Overall survival stratified by response status. Dashed curve = patients with overall success from either first- or second-line therapy ($n = 44$); solid curve = those without such a response ($n = 106$). The probability of surviving 2 years or more for the 44 patients with overall success was 71% (95% confidence interval [CI] = 58% to 85%), compared with 35% (95% CI = 27% to 46%) for the 106 without such a response. Two-sided log-rank tests (9) were used for statistical comparisons.

Overall, 155 (47%, 95% CI = 42% to 52%) of the 330 courses were assessed as successful. Two consecutively successful courses (i.e., the endpoint that we designated as overall success) were

observed in 35 (23%, 95% CI = 17% to 31%) patients by means of first-line treatment (Table 3)—four with CVD, seven with KA/VE, 14 with TEC, and 10 with TEE. An additional nine patients had an overall success with their second-line treatment (i.e., had response histories of FSS or SFSS—two with CVD, five with KA/VE, two with TEC, and zero with TEE). Thus, a total of 44 (29%, 95% CI = 23% to 37%) patients met the response threshold that we defined as likely to be associated with unequivocal patient benefit. The major criterion for overall success was a PSA reduction of 80% from baseline, with no subsequent increase, at 16 weeks. We did not measure serum levels of PSA every 4 weeks, and so we cannot rigorously report PSA response by the consensus criteria (14) of a 50% reduction maintained for 4 weeks. However, the consensus definition of a PSA response would be close to the rate of success by our first-course criteria (see above), which was achieved by 99 patients (66%, 95% CI = 58% to 73%).

For the entire cohort, median time from initiation of chemotherapy to progression was 4.9 months (95% CI = 4.1 to 5.9 months; range = 1–42 months). Median overall survival from registration, which is essentially identical to cause-specific survival in this cohort, was 22 months (95% CI = 19 to 26 months) (Fig. 2, A). Estimated overall survival rates at 2, 3, 4, and 5 years, respectively, were 45% (95% CI = 38% to 54%), 26% (95% CI = 20% to 35%), 15% (95% CI = 11% to 23%), and 10% (95% CI = 5% to 16%). The median survival from the initial diagnosis of prostate cancer was 6.3 years (95% CI = 5.6 to 7.6 years; range = 1–19 years). Thus, prolonged survival after diagnosis was not rare in this cohort, even though it included many patients with nonlocalized disease at diagnosis.

As we have reported previously (15), duration of response to hormone therapy (i.e., time from initiation of sustained hormone therapy to registration) was strongly related to survival after initiation of chemotherapy (Fig. 2, B). In a multivariable Cox model analysis, disease volume at registration was also statistically significantly associated with survival, as was clinical response. The 44 patients with overall success (all of whom had a PSA reduction of at least 80% from baseline) had a median survival of 30 months (95% CI = 26 to 40 months), and the 106 patients without such a response had a median survival of 19 months (95% CI = 17 to 22 months) (difference = 11 months, 95% CI of the difference = 4.9 to 19.6 months; $P = .001$) (Fig. 2, C).

Deliverability and Adverse Events

Many patients did not complete the treatment algorithm as planned. Of the 115 patients who did not have two consecutive successful courses with first-line treatment and, therefore, should have been randomly assigned to a second-line treatment, only 75 (65%) were actually randomly assigned to a second-line treatment and treated. Six (16%, 95% CI = 8% to 31%) of the 37 patients initially assigned CVD progressed in the first 8 weeks, and thus they were no longer fit for chemotherapy. Also noteworthy was the high rate of intolerable toxic effects (nine [23%] of the 39 patients, 95% CI = 13% to 38%) among patients initially assigned TEE; most of these events were thromboembolic events. Data related to all 40 patients who were not assigned a second-line treatment are summarized in Table 4.

Adverse events were recorded according to the Common Toxicity Criteria, version 2.0 (available at http://ctep.cancer.gov/reporting/ctc_archive.html). Overall, there were 110 adverse

Table 4. Reasons for patients not proceeding to second-line treatment*

Initial regimen	No. of patients			Total
	Excessive toxicity	Disease progression	Physician decision	
CVD	2	6	1	9
KA/VE	4	1	3	8
TEC	4	1	3	8
TEE	9	2	4	15
Total	19	10	11	40

* Number of patients is given for each category of reasons that patients did not proceed to salvage treatment (even though they did not have consecutively successful courses with first-line treatment). CVD = cyclophosphamide, vincristine, and dexamethasone; KA/VE = ketoconazole plus doxorubicin alternating with vinblastine plus estramustine; TEC = weekly paclitaxel, estramustine, and carboplatin; TEE = paclitaxel, estramustine, and etoposide.

events of grade 3 or greater among 68 (45%, 95% CI = 38% to 53%) of the 150 patients (Table 5). Two deaths were attributed to treatment, one from a stroke and one from secondary leukemia. The patient who died of a stroke had been on long-term anticoagulation therapy with warfarin because of a previous stroke. In the first few days of treatment, he complained of difficulty swallowing. His anticoagulation therapy was then stopped so that a diagnostic upper endoscopy examination could be performed, and he had a fatal stroke while off anticoagulation therapy. The patient who died of leukemia had cytogenetic test results consistent with etoposide-induced acute myelogenous leukemia.

Grade 4 events were relatively uncommon (i.e., observed in 13 of 330 courses; 4%, 95% CI = 2% to 7%) and were usually related to thromboembolism. Overall, 20 (13%, 95% CI = 9% to 20%) of 150 patients had thromboembolic events of grade 3 or 4, even though nearly all patients received prophylactic low-dose warfarin and many received both warfarin and aspirin. The observed burden of toxicity from therapy was in keeping with prior experience with these regimens (6–8,15).

Response-Based Selection Analysis

There are many ways to analyze the response data for various selection goals. As a starting point, we considered the simple success rate for each regimen, i.e., the number of treatment courses judged as a success, divided by the total number of courses for which a particular regimen was the assigned treatment. The observed per-course success rates with the regimens we investigated were 57% (95% CI = 47% to 67%) for TEC, 52% (95% CI = 42% to 63%) for KA/VE, 45% (95% CI = 34% to 55%) for TEE, and 28% (95% CI = 18% to 40%) for CVD (Table 3). By this simple analysis, TEC emerged as the most active regimen.

The simple per-course success rate ignores differences between initial success and overall success (which were defined by different criteria), the difference between the first-line and second-line setting, and the treatment sequence—all of which are potentially of interest. The first two issues are addressed by our conditional logistic regression model, which represents the probability of response conditionally, explicitly accounting for course, current treatment, and patient history, in a way that recapitulates typical

Table 5. Numbers of adverse events of grade 3 or greater*

Event	Grade 3	Grade 4	Grade 5
CNS cerebrovascular ischemia	0	0	1
Secondary leukemia	0	0	1
Thrombosis/embolism	17	3	0
Dyspnea	0	2	0
Ureteral obstruction	0	2	0
Febrile neutropenia	4	1	0
Vomiting	4	1	0
Confusion	1	1	0
Hypoglycemia	1	1	0
Delusions	0	1	0
Musculoskeletal, fracture	0	1	0
Transfusion: PRBCs	11	0	0
Fatigue	7	0	0
Infection without neutropenia	7	0	0
Stomatitis/pharyngitis	4	0	0
Cardiac-ischemia/infarction	3	0	0
Dehydration	3	0	0
Nausea	3	0	0
Neuropathy—sensory	3	0	0
Supraventricular arrhythmias	3	0	0
Bone pain	2	0	0
Hypertension	2	0	0
Mood alteration—anxiety agitation	2	0	0
Anorexia	1	0	0
Bilirubin	1	0	0
Cardiac left ventricular function	1	0	0
Catheter-related infection	1	0	0
Catheter-related thrombosis	1	0	0
Colitis	1	0	0
Constitutional symptoms	1	0	0
Diarrhea: patients without colostomy	1	0	0
Edema	1	0	0
Hand-foot skin reaction	1	0	0
Hematuria	1	0	0
Hyperglycemia	1	0	0
Neurology: pseudobulbar palsy	1	0	0
Pleural effusion	1	0	0
Transfusion: platelets	1	0	0
Weight loss	1	0	0
Total	93	13	2

* CNS = central nervous system; PRBC = packed red blood cells.

clinical reasoning. This model is one approach to the analysis of a “dynamic treatment regime” (16,17).

Using all response data for all 330 courses of treatment, we fit the logistic regression model for all 13 parameters (Table 6). These results showed that 1) as initial treatment in course 1, TEC was the best treatment, and CVD was the worst treatment; 2) CVD was the best treatment for producing overall success that was conditional on initial success (i.e., response quality); and 3) KA/VE produced the most responses in the second-line setting after failure of a different treatment given first-line (i.e., KA/VE was the least cross-resistant treatment). The least successful treatment given as a second-line treatment was TEE. Disease volume was indeed an important predictor of survival, as shown by the fitted value of the parameter *c*, which had final value 0.627 (giving an odds ratio for response of patients with low-volume versus high-volume disease = 1.87, 95% CI = 1.12 to 3.14, *P* = .018).

Table 6. Final logistic regression model for conditional probability of response*

Treatment	Initial response rate, m_i	Response quality, a_i	Cross-resistance, b_i
<i>Response probability as a function of treatment and prior history† (95% CI)</i>			
CVD	-1.4 (-2.19 to -0.64)	1.1 (-0.23 to 2.42)	0.05 (-2.34 to 2.44)
KA/VE	0.34 (-0.31 to 0.99)	-0.99 (-1.9 to -0.07)	-0.19 (-1.65 to 1.26)
TEC	0.75 (0.07 to 1.42)	-1.05 (-1.92 to -0.17)	-1.37 (-3.02 to -0.28)
TEE	0.19 (-0.46 to 0.84)	-0.66 (-1.72 to 0.39)	-3.30 (-5.54 to -1.06)
<i>ORs for pairwise comparisons‡ (95% CI)</i>			
CVD vs KA/VE	0.17 (0.06 to 0.46)	8.01 (1.60 to 40.03)	1.28 (0.08 to 20.71)
TEC vs KA/VE	1.50 (0.60 to 3.74)	0.94 (0.27 to 3.33)	0.31 (0.03 to 2.78)
TEE vs KA/VE	0.86 (0.35 to 2.11)	1.38 (0.34 to 5.56)	0.04 (0.0 to 0.64)
TEC vs CVD	8.67 (3.23 to 23.27)	0.12 (0.02 to 0.57)	0.24 (0.01 to 4.39)
TEE vs CVD	4.97 (1.88 to 13.16)	0.17 (0.03 to 0.93)	0.04 (0.0 to 0.92)
TEE vs TEC	0.57 (0.23 to 1.42)	1.47 (0.37 to 5.76)	0.14 (0.01 to 2.33)

* CVD = cyclophosphamide, vincristine, and dexamethasone; KA/VE = ketoconazole plus doxorubicin alternating with vinblastine plus estramustine; TEC = weekly paclitaxel, estramustine, and carboplatin; TEE = paclitaxel, estramustine, and etoposide; OR = odds ratio; CI = confidence interval.

† Estimated values and their 95% confidence intervals (i.e., from the fitted model) for response probability as a function of treatment and prior history are shown. Model parameters represent the initial response rate (m_i), the response quality (a_i), and the cross-resistance (b_i) for each treatment in each course of therapy. Larger values of m_i correspond to a higher overall response probability with each treatment (t). Larger values of a_i correspond to a higher second consecutive response probability after an initial response with t . For a given history, larger negative values of b_i correspond to a greater reduction in response probability.

‡ Pairwise comparisons of the initial treatment, response quality, and cross-resistance effects.

Using the fitted model, we then computed the model-based success probability for each combination of treatment and outcome history, which allows for a direct comparison of the observed per-course success rates with those calculated on the basis of the logistic regression model (Table 7). For example, among the 17 patients who had a treatment failure in course 1 and received KA/VE in course 2 (i.e., outcome history F and randomly assigned to KA/VE as a second-line treatment), eight responses were observed (47%, 95% CI = 26% to 69%). The comparable model-based weighted average estimate of the conditional course 2 probability of response was 57%. Inspection of Table 7 indicates that the model fits the observed values reasonably well.

The response data from the trial lead to the following hypotheses about the treatments that we investigated. First, TEC was the most active treatment overall; i.e., it is the treatment that would be selected for phase III evaluation. Second, if one were to pursue the intuitive strategy of starting with the treatment with the highest probability of overall success and then giving the treatment with least cross-resistance (i.e., the treatment with the most favorable value of parameter b_i) second-line, TEC as the first-line treatment

followed by KA/VE as the second-line treatment would make the best use of the regimens we investigated.

Survival-Based Selection Analysis

The treatment assignment algorithm was based on clinically observable responses, and our initial analysis of the design concentrated on inferences that were based on observed responses. The trial data are mature (i.e., 91% of patients have died), and so it is possible to analyze the trial’s selection properties in terms of survival and also to determine whether the hypotheses generated from the response data are reinforced by the survival outcome data. Any adaptive treatment design must use some indicator of patient benefit that is clinically apparent in a timely fashion. In the context of this specific trial, it was of interest to determine if the response thresholds that we defined reliably predicted survival in this patient population.

In a standard Cox model for survival that included baseline covariates (Table 2) and the initially assigned first-line therapy, none of the treatments were statistically significantly associated with survival (data not shown). In fact, the factor most strongly associated with survival was the time from initiation of hormone

Table 7. Observed and model-based response probabilities for each treatment and outcome history in this trial*

Regimen	First-line therapy				Second-line therapy							
	Untreated		S		F		SF		FS		SFS	
	E	M	E	M	E	M	E	M	E	M	E	M
CVD	0.27	0.24	0.40	0.51	0.13	0.20	0.13	0.22	1.0	0.43	1.0	0.51
KA/VE	0.69	0.62	0.29	0.39	0.47	0.59	0.00	0.57	0.63	0.33	NA	0.43
TEC	0.68	0.72	0.56	0.48	0.60	0.49	0.64	0.62	0.20	0.23	0.14	0.40
TEE	0.59	0.60	0.48	0.43	0.17	0.14	0.25	0.26	0.00	0.11	0.00	0.14

* The empirical (E) per-course response probability (from Table 3) is compared with the model-based (M) estimate. The model-based value represents the weighted average accounting for patients with high or low disease volume. CVD = cyclophosphamide, vincristine, and dexamethasone; KA/VE = ketoconazole plus doxorubicin alternating with vinblastine plus estramustine; TEC = weekly paclitaxel, estramustine, and carboplatin; TEE = paclitaxel, estramustine, and etoposide; NA = not observed.

therapy to registration ($P = .004$), with a longer duration of prior hormone therapy associated with better survival (data not shown).

When both first-line and second-line treatments were considered, no statistically significant differences in survival were observed among the 12 two-treatment strategies evaluated. This result was not surprising because small numbers of patients were treated with each strategy and because this investigation was designed to be a hypothesis-generating, not a hypothesis-testing, trial. Nonetheless, some trends were observed that could serve as the basis for selection. The best survival was observed with the two-treatment combination of TEC followed by KA/VE ($n = 26$), which gave a median overall survival of 26 months (95% CI = 22 to 38 months), compared with 21 months (95% CI = 18 to 24 months) for the other 11 regimen combinations ($n = 124$ patients; $P = .32$). The worst survival was observed with the two-treatment strategy of CVD followed by TEE ($n = 20$), which gave median overall survival of 18 months (95% CI = 11 to 28 months), compared with 22 months (95% CI = 20 to 26 months) for the other 11 regimen combinations ($n = 130$ patients; $P = .44$). Thus, we generate the selection hypothesis that, of the treatments we investigated, the most successful sequence is TEC as a first-line treatment, followed by KA/VE as the second-line treatment. It should be noted that the two-stage strategy selected by use of the response data was the same as that selected by use of the survival data. The response thresholds that we defined do indeed appear to be useful indicators of patient benefit.

Discussion

The survival observed for all patients treated in this trial confirms that with available therapy the median survival of patients with castration-resistant prostate cancer is nearly 2 years, even in a cohort in which most patients had advanced bone or visceral disease. More importantly, our experience consistently demonstrates (15) that approximately 10% of patients are alive at 5 years, an outcome that was essentially unheard of a decade ago. Indeed, in the landmark studies of docetaxel reported by Petrylak (2) and Tannock (3) in 2004, there were no survivors beyond 48 months in either trial. The improvement in survival can be attributed to many factors, including stage migration driven by closer surveillance, increased use of chemotherapy, the availability of multiple active regimens with some activity in the salvage setting (as demonstrated in this study), and the availability of bone consolidation strategies, such as targeted radiotherapy among patients who respond to chemotherapy (18).

Among the four treatments that we investigated (all from the era before docetaxel treatment was available), we found evidence that some patients responded to treatments given as second-line regimens, even when the first-line treatment was more active overall. For example, in one patient, TEC (the most active treatment in this trial) failed but CVD (the least active treatment) produced an overall success. Of course, such an observation simply reflects the clinically apparent fact that some treatments are better suited for some patients. Although individual patients cannot yet be

matched to individual treatments, the results of this trial allowed us to advance the hypothesis that use of TEC as the first-line treatment and use of KA/VE as the second-line treatment is the optimal two-stage sequence of the four regimens that we investigated. It is noteworthy that the two-stage sequence with the most favorable response profile was also the approach associated with the best overall survival, and likewise, the worst combination, as judged from the response data, was in fact associated with the worst survival. These results indicate that the response thresholds that we defined—namely, an 80% reduction in PSA level maintained for 8 weeks, conventional partial response in any measurable disease, and resolution of cancer-specific symptoms—are indeed clinically meaningful and that reasonable selection hypotheses can be generated from an adaptive therapy approach.

In our view, the results of this trial provide an objective basis for phase III evaluation of TEC versus the current standard of single-agent docetaxel. Moreover, the results indicate that the contribution of carboplatin to treatment of patients with androgen-independent prostate cancer may have been underappreciated. Thus, we interpret these results as also providing a strong rationale for the development of carboplatin-containing combination treatments, and in fact such efforts have begun (19).

The scientific goals of cancer therapy development are evolving. In virtually every case, new therapies are now introduced into a context of established treatment(s) and into the context of conceptually similar interventions being developed in parallel. As such, investigators are obliged not only to determine whether a new treatment has activity in some disease state (the traditional phase II objective) but also to investigate the much more difficult issue of how new treatments should be integrated with existing treatment(s)—i.e., questions about the combination and sequence of treatments. Because definitive randomized comparisons of all promising therapies for all disease states in oncology cannot be performed, promising therapies need to be identified by the use of a selection methodology. The algorithm and analysis used in this study appears to be a useful method for the selection of promising therapies. This design can identify potentially non-cross-resistant treatments (i.e., treatments that are active as second-line approaches) and thus objectively contribute to the selection of treatment combinations and sequences that warrant further clinical investigation. Importantly, this design also promotes early switching away from treatment not producing a response, serving the need to find the most active treatment for the individual patient (even if the regimen identified is not the “best” regimen from the perspective of the entire treated cohort).

This study had several limitations. This was a single-institution study. The patient population at our referral institution is rather unusual, in that a typical individual patient can seek out health care beyond his or her immediate geographic area and is also highly motivated to receive even logistically complex or toxic treatment; clearly, our results must be interpreted in this context. A large number of patients dropped out—40 (27%) of the 150 patients—and so a more detailed statistical analysis accounting for potentially informative dropouts is certainly worthwhile. Because this is the first use of our analysis methods, the reliability of inference from

our analysis has not been established; i.e., the hypotheses that we have generated have not yet been tested. There are also methodologic variants that might be more appropriate in other settings involving other treatment allocation algorithms. For example, acceptable first-line treatments might be well established, or some treatment sequences might incorporate closely related treatments and thus be highly cross-resistant. When methods become available to match individual patients to specific treatments, there will be little need for selection methods like the one that we report in this article.

In summary, we have reported the application of an adaptive therapy approach that formalizes typical clinical practice and reasoning. The treatment allocation algorithm mandated early switching away from treatments not producing an early response, and simultaneously investigated 12 distinct two-stage strategies. Analysis of the results using a statistical model that borrows strength across patients and strategies (i.e., patient outcomes from different strategies contribute to the calculation of the model's parameters) allowed the generation of selection hypotheses. Selection of the optimal two-stage strategy that was based on response data was congruent with selection based on survival data. Still, issues of treatment combination and sequence remain difficult areas for clinical trial design, even as the proliferation of active agents and regimens makes these questions increasingly important.

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Notes

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