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LONG-TERM OUTCOME FOR MEN WITH ANDROGEN INDEPENDENT PROSTATE CANCER TREATED WITH KETOCONAZOLE AND HYDROCORTISONE

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ABSTRACT

Purpose: The combination of high dose ketoconazole and hydrocortisone (HDK) is active against androgen independent prostate cancer (AIPC). Median response times with HDK tend to be brief but a significant minority of AIPC patients benefit with extended responses. Well characterized response and survival information, especially in the cohort of patients who experience these longer, more durable, responses has not been previously reported. Characterization of this subgroup is of particular interest since men with long-term responses derive the greatest benefit from HDK therapy.

Materials and Methods: The medical records of 78 patients with AIPC treated with HDK between March 1991 and February 1999 were retrospectively reviewed. Baseline clinical and laboratory factors predictive of prolonged response and survival were identified.

Results: The median baseline prostate specific antigen (PSA) before the initiation of HDK was 25.1. The number of patients with zero, 1 to 3, and more than 3 lesions on bone scan were 25, 35 and 18, respectively. Median and mean time to PSA progression was 6.7 and 14.5 months. Median and mean survival time was 38.0 and 42.4 months, respectively. Response time and survival were highly correlated ($r = 0.799$). A total of 34 (44%) men had a greater than 75% decrease in PSA. The median survival times in men with more vs less than a 75% decrease were 60 vs 24 months, respectively. In a Cox proportional hazard regression, prolonged survival was predicted by percent PSA decrease, extent of disease on bone scan and baseline PSA.

Conclusions: Ketoconazole can induce prolonged responses, occasionally lasting for years. Long responses are more likely to occur in men initiating HDK earlier in the course of disease before the cancer burden becomes excessive.

KEY WORDS: ketoconazole, prostatic neoplasms, prostate-specific antigen, survival

High dose ketoconazole in combination with hydrocortisone (HDK) is an active regimen in the treatment of androgen independent prostate cancer (AIPC). Studies demonstrating HDK efficacy in AIPC date back to the pre-prostate specific antigen (PSA) era.[1,2] In those early years, HDK was also used in the treatment of patients with hormone sensitive disease.[3,4] After the discovery of PSA, trials incorporating PSA as a response indicator to assess HDK in AIPC confirmed high PSA response rates, although the reported median response times were generally short.[5,6] These studies also identified a subset of patients who experienced more extended responses. Survival information, especially in the cohort of patients demonstrating more durable responses has not been reported. We retrospectively reviewed 78 patients with AIPC treated with HDK from a medical oncology practice specializing in prostate cancer attempting to identify a cohort of men who would derive the most benefit from HDK.

MATERIALS AND METHODS

Patient selection for inclusion. All patient charts at Prostate Oncology Specialists, a medical oncology practice specializing in prostate cancer, were reviewed for study inclusion. There were 5 criteria used for selection. 1) Hormone refractory prostate cancer as defined by 3 consecutive increases in PSA despite castrate testosterone levels and previous therapy with at least 1 antiandrogen. 2) HDK administered for a minimum of 2 months. Patients receiving HDK for less than 2 months and who were taken off therapy because of HDK induced toxicity were included in the study and tabulated as nonresponders failing at 2 months. 3) No additional anticancer agents other than hydrocortisone administered concomitantly. 4) Adequate clinical and laboratory information available for review. 5) To ensure adequate followup only patients started on HDK before February 1999 were included.

Treatment schema. High dose ketoconazole was initiated at a dose of 200 mg every 8 hours on an empty stomach. If no toxicity was encountered during the first 7 days of treatment the dose was increased to 400 mg every 8 hours. Patients unable to forego antacid medication were not treated with HDK. Patients were routinely administered hydrocortisone at a starting dose of 20 mg twice a day with food. In most patients, the hydrocortisone dose was decreased to 20 mg with breakfast and 10 mg with dinner after 1 month of HDK therapy. In a few patients the standard dose of HDK of 1,200 mg a day was not tolerated. In such patients a dose reduction to the starting dose of 200 mg 3 times a day permitted them to continue on HDK therapy and remain on study.

Clinical monitoring schema. Since this was a retrospective analysis, there were no specific study criteria. However, all

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TABLE 1. *Descriptive statistics for 78 men treated with HDK*

Variable	Mean	Median	Min	Max	Upper Quartile
Age start HDK	69.5	70.4	50.4	87.8	74.4
HB Rx mos	36.6	28.5	3	129	57
Dx to Rx mos	62.1	57.2	8.6	167.1	84.2
Baseline PSA	121.9	25.1	0.06	1,867	97
Baseline ALP	126.5	85.5	29	761	127
Baseline Hct	36.9	37.2	21	44.3	39.2
Response time (mos)	14.5	6.7	1	91	17.0
PSA % decrease	56	69	0	100	93
Survival (mos)	42.4	38	4	116	61

every 6 to 12 months and at the time of PSA progression. Patients with measurable adenopathy on computerized tomography had repeat scans periodically and at the time of disease progression. PSA levels were relied upon heavily as the main clinical indicator of response or progression and as such were generally checked monthly. Patients with responses greater than 12 months had PSA levels drawn at 2 to 3 months intervals. Hepatic panels and chemistry panels were initially checked monthly because of HDK's known potential for hepatotoxicity. Physical examination was done at baseline and repeated every 6 months. The majority of patients had Gleason scores reviewed by 1 of a small group of nationally known pathologists. No patient developed clinical progression (changes in bone scan or computerized tomography) without first manifesting progression by PSA criteria. PSA decreases of 50% and 75% were only considered valid if maintained for at least 4 weeks.[7]

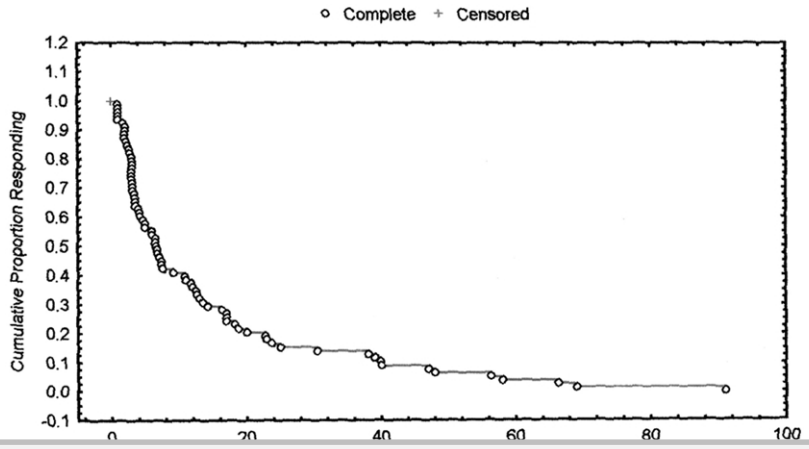
Study definitions. Baseline is a laboratory or clinical finding which immediately preceded the initiation of HDK. Response Time is the time from the initiation of HDK until the first of 2 consecutive PSA values that are 50% and at least 2 ng/dl greater than the nadir PSA value.[8] Progression, time to progression, or time on HDK as used in the paper are all synonymous with Response Time. Survival time is the time from initiation of HDK to the time of death from prostate cancer. Hormone blockade treatment time (HB Rx Time) is the time from starting hormone blockade to the time AIPC is diagnosed using the criteria previously described. PC diagnosis to HDK Time (Dx to Rx) is the time from PC diagnosis to the time of starting HDK. Bone scan stage is defined as stage 1 —no bone metastasis, stage 2—1 to 3 bone metastases and stage 3—4 or more bone metastases. Percent PSA decrease is defined as the percent decrease in PSA from baseline to nadir.

Statistical issues. All statistical calculations were performed on Statistica™. The survival variable is censored, that is, it contains survival times and censored survival times. As a consequence its mean, median, and correlations are somewhat biased estimates of population values. These estimates are used only for rough descriptive and exploratory purposes. Kaplan-Meier survival curves and Cox regressions are used to deal with the biases resulting from censoring. The Kaplan-Meier curves are used primarily to compare survival in subpopulations defined by specified ranges of a single variable. Cox regression is used to adjust survival comparisons for potential confounders. Step-down Cox regression is used to find significant risk factors and identify potential confounders.

For the survival time, patients suffering a nonprostate cancer death, patients lost to followup, patients who stopped HDK for reasons of toxicity, and patients alive at the end of the study were censored. The same criteria were used for response time end point except patients alive at the end of the study is replaced by patients responding at the end of the study.

TABLE 2. *Characteristics of 78 men treated with HDK*

	No. Men
Neg bone scan	25
1–3 Lesions on bone scan	35
Greater than 3 lesions on bone scan	18
Still on treatment	3
Stopped responding to HDK	62
Stopped HDK for toxicity while responding	5
Lost to followup while responding	3
Treatment changed while responding	1
Died of unrelated causes while responding	4
Died of unrelated causes after progression	1
Died of prostate Ca	61



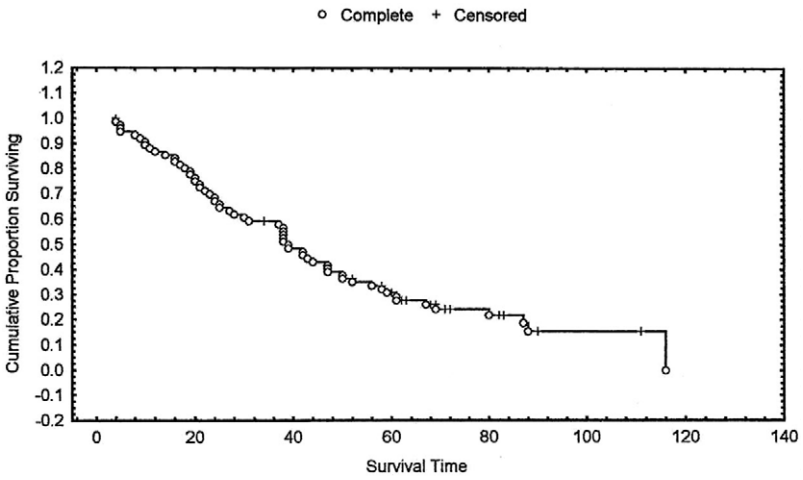


FIG. 2. Kaplan-Meier representation of survival for all 78 patients

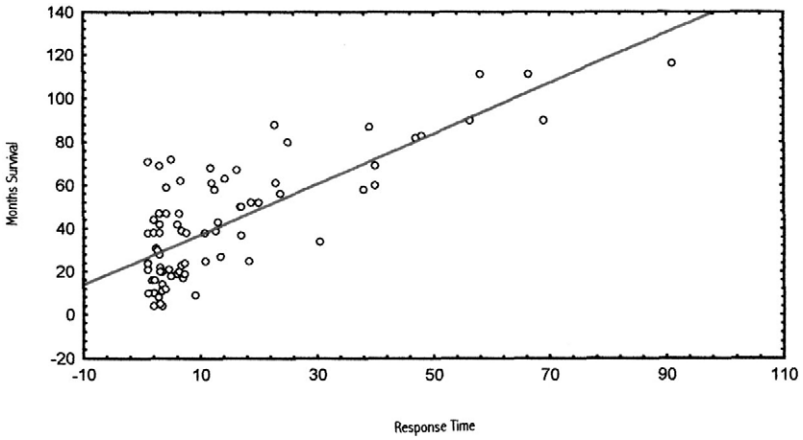


FIG. 3. Months survival vs months response time

RESULTS

In a chart review of 1,200 patients, 78 patients met the study inclusion criteria previously defined. Most excluded patients were deemed ineligible because they had not received HDK. Some patients were excluded due to insufficient data for analysis or because of the simultaneous administration of additional anticancer agents. Descriptive statistics for baseline and response data for the 78 patients that form the basis of this study are summarized in tables 1 and 2. As of March 2004, 75 of 78 patients had progressed as defined by the progression criteria defined in the materials and methods section. The median and mean response time for all 78 patients was 6.7 and 14.5 months, respectively. The median and mean survival times were 38.0 and 42.4 months, respectively. Kaplan-Meier representation of response time for all 78 patients is portrayed in figure 1. Kaplan-Meier representation of overall survival is portrayed in figure 2. Correlation between response time and survival is shown in figure 3.

Nine laboratory and clinical factors, which were possibly predictive of response time and survival, were evaluated in univariate analysis with the Spearman coefficient. Seven factors had an r value of greater than 0.23 ($p < 0.05$) for predicting response time and survival (table 3). For response time the 7 factors were HB RX time, DX to RX, log of baseline PSA, alkaline phosphatase (ALP), bone scan stage, percent PSA decrease and Gleason score. For survival the predictors were the same except that Gleason score was lost as a predictor and baseline hematocrit (Hct) was added. Step-down Cox proportional hazard regression analysis starting with these 7 predictors indicated that for response time, 3 factors, the log of baseline PSA, HB Rx Time and percent PSA decrease were predictive. For survival log of baseline PSA, bone scan stage and percent PSA decrease were predictive (table 4).

TABLE 3. *Univariate correlations of response time and survival*

Variable	Response		Survival	
	Spearman R	p Value	Spearman R	p Value
Age start HDK	0.21	0.07	0.16	0.16
HB Rx time	0.25	0.03	0.29	0.01
Dx to Rx time	0.28	0.01	0.24	0.03
Log baseline PSA	−0.35	0.001	−0.43	<0.001
Baseline ALP	−0.25	0.03	−0.32	0.004
Baseline Hct	0.20	0.07	0.23	0.04

TABLE 4. *Predictors of response time and survival using Cox regression analysis*

Variable	Response		Survival	
	t Value	p Value	t Value	p Value
Log base PSA	3.56	<0.001	3.48	0.0005
Bone scan stage	—	Not significant	2.80	0.005

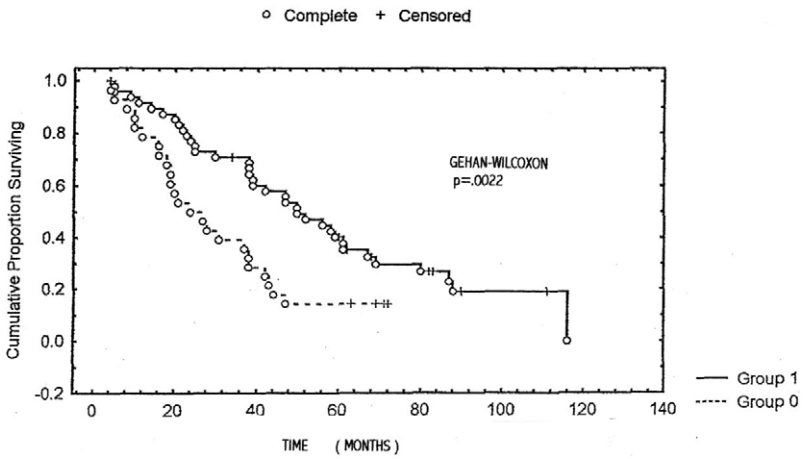


FIG. 4. Kaplan-Meier representation of survival time. Group 0 denotes men with less then 50% decrease in PSA. Group 1 denotes men with greater than 50% decrease in PSA.

We then evaluated percent decrease in PSA as a categorical rather than a continuous variable for predicting survival. Kaplan-Meier analysis indicated that a greater than 50% decrease predicted increased survival (fig. 4). However, when patients with greater than a 50% decrease were split into groups constituted by those 50% to 74% vs 75% to 100%, men with a 50% to 74% PSA decrease had a survival time similar to the men with a PSA decrease of less than 50% (fig. 5). This suggests that survival may not be linearly related to percent decrease. These Kaplan-Meier analyses can be faulted because they ignore possible confounding with other important predictors of survival such as baseline PSA, and bone scan stage. To deal with this and the nonlinearity, percent decrease was categorized into 4 equal width intervals and used as a categorical variable in a Cox regression to predict prostate cancer death risk after adjusting for log baseline PSA, and bone scan stage. Figure 6 is a plot of the resulting relative risks. This figure suggests that it is only the larger values of percent decrease, those in the range of 0.75 to 1, that affect risk. For this category the risk reduction is about a factor of 3.4. Only this category is significantly different ($p < 0.001$) from the reference category which is the first category.

In terms of toxicity, 5 men who were responding to HDK stopped treatment early while still benefiting from an ongoing PSA response after 12, 24, 25, 34 and 39 months of therapy. The reason for early discontinuation of HDK was excess lassitude and tiredness in all 5 cases. No patients died or developed severe toxicity from HDK.

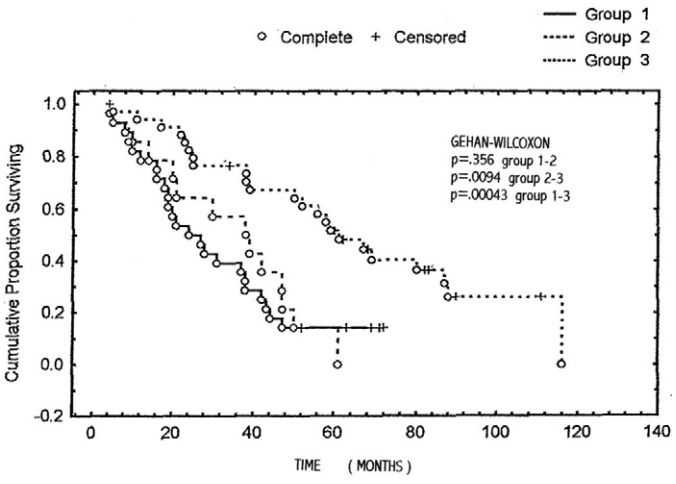
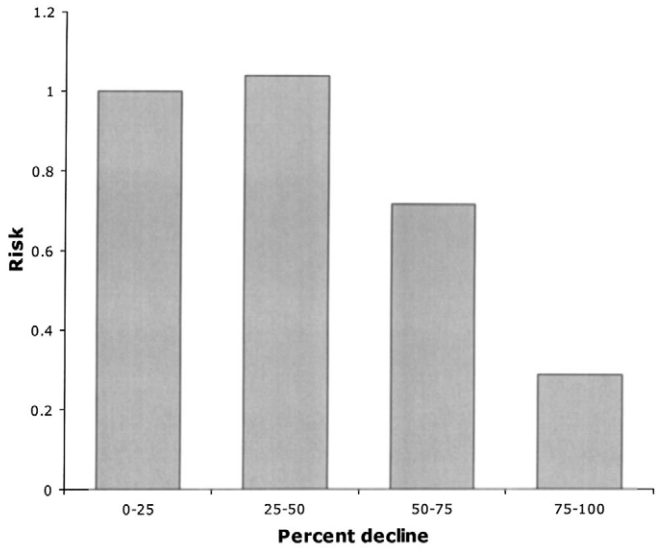


FIG. 5. Kaplan-Meier representation of survival time. Group 1

DISCUSSION

This 78 patient series is notable in 2 distinct ways. First followup greater than 13 years enables us to use actual, not projected, measurements of survival and response time. This longer period of observation demonstrates that a significant number of men treated with HDK remained on treatment for several years. For example, men in the upper quartile of response time had responses lasting for a minimum of 1 and a half years. The longest response, which is still ongoing, has lasted 91 months. Long response durations tracked closely with long survival times.

A second notable aspect of this patient series suggests a possible reason for these relatively long response and survival times. Our patient cohort contains a significant number of men who developed AIPC before the development of a



pd	risk
0-25	1
25-50	1.04
50-75	0.72

positive bone scan, while those men who did have a positive bone scan tended to have a limited extent of metastatic bone disease, ie less than 4 lesions. This may explain our somewhat long median response time of 6.7 months compared with other patient series.[9] Cox regression analysis in table 4 did indicate that a more favorable bone scan stage, and a baseline PSA less than 25 ng/ml (the median for the 78 patients), predicted longer survival. The median response time of the men who started HDK with positive bone scans was 4.8 months, which is consistent with other reported series using HDK therapy.

Percent decrease in PSA in response to therapy predicted prolonged response and survival. The degree of PSA decrease in response to therapy as an early indicator for predicting prolonged survival in androgen independent prostate cancer has been reported in multiple studies.[10,11] Percent PSA decrease in response to therapy is an elegant solution to the historical problems related to judging drug efficacy in AIPC where measurable disease only occurs in a minority of patients. Unfortunately a consensus for using PSA response as a surrogate for survival is still lacking.[12]

Our study finding that a 50% or greater decrease in PSA in response to therapy predicts prolonged survival was in line with other much larger and validated trials of HDK.[13,14] However, further analysis of our data indicated that only the patients with a 75% or greater decrease in PSA truly had a longer survival. The reason that a 50% decrease also predicted prolonged survival was because the 50% demarcation by its very nature also incorporated patients with a 75% or greater decrease in PSA. Clearly a 75% decrease is a strong predictor of survival when it is able to impute significance to a 50% decrease, a degree of decrease that is substantially diluted with the nonpredictive information contained in the interval between 50% and 74%.

There seems to be a lack of awareness in the literature that using overlapping variables such as 50% and 75% could in some cases indicate falsely that decreases in PSA that reach the 50% threshold will necessarily correlate with increased survival. When we examined the survival of patients falling into the quartile of a 50% to 75% decrease, we found no increase in survival compared with men who had less than a 50% decrease.

The shortcomings of this study are those characteristic of all retrospective studies. One confounding factor that may have affected our results was our policy regarding the antiandrogen withdrawal response (AAWR). In the majority of cases, our usual approach was not to delay starting HDK after stopping the preceding antiandrogen, although in a minority of cases an attempt at AAWR was implemented before HDK was started. Proceeding directly to HDK without first performing an AAWR was adopted because of the relatively infrequent occurrence (20% to 25%) of the antiandrogen withdrawal response, and its relatively short mean duration of about 3 to 5 months that has been previously reported.[15,16] A recent randomized prospective trial showed only a 13% response rate.[17] We performed an analysis of response time and survival in our own patient series (data not included) and we did not find a significant difference between AAWR followed by HDK compared with no AAWR ie immediate HDK. This finding, the absence of a survival difference between these 2 different approaches, has been previously reported.[17]

In the process of patient selection for study inclusion, every attempt was made to include all potentially eligible candidates. Surprisingly we found that relatively few patients had stopped HDK for reasons of toxicity. The most common reason for early discontinuance was lassitude, a well-known effect of ketoconazole.[18] We have had some success counteduced malaise by attempting to reverse the hypogonadally induced sarcopenia through a muscle building program under the supervision of qualified trainers. A group in Canada has used this approach successfully to counteract lassitude in men treated with hormone blockade.[20]

CONCLUSIONS

Retrospective review of 78 patients with androgen independent prostate cancer treated with HDK showed that the men in the upper quartile of PSA response had durable responses lasting from 17 months to more than 7 years. The men most likely to experience extended responses and longer survival were those who started HDK with minimal or no bone scan involvement and a low baseline PSA. PSA decrease of 75% or greater in response to HDK therapy predicted better survival compared with men with less than a 75% decrease.

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