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High-Dose Ketoconazole to Untreated Stage D Prostate Cancer

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Abstract—*Eleven previously untreated patients with stage D prostate cancer were treated with ketoconazole in a dosage of* 400 *mg p.o. every* 8 *h. s-Testosterone was used as a measure of antiandrogen effect. Nine patients had a reduction in s-testosterone to castrate levels* (<2.9 *nmol/l*) *within* 3 *days. In the remaining two patients, dose escalation of ketoconazole to* 400 *mg every* 6 *h did not lead to sufficient reduction in s-testosterone. Two patients had a complete response and four patients had a partial response of* 6/11. *Additionally, two patients had bone pain relief without normalization of acid phosphatase. Side-effects and adverse reactions were prominent, causing discontinuation of the treatment in nine patients. It is concluded that high-dose ketoconazole is effective in disseminated prostate cancer, but the high frequency of side-effects makes it less attractive than conventional hormone manipulations like castration or estrogens.*

INTRODUCTION

KETOCONAZOLE, an antifungal imidazole derivative, has been shown to block both testicular and adrenal androgen biosynthesis by inhibition of the cytochrome P-450-dependent 17,20-lyase [1], resulting in a reduction of plasma androgen levels, especially testosterone [2]. High-dose ketoconazole has been reported to reduce bone pain and normalize serum acid phosphatase in patients with bone metastases from prostate cancer [3].

We report here the results of high-dose ketoconazole in 11 previously untreated patients with stage D prostate cancer.

MATERIALS AND METHODS

Previously untreated patients with histologically proven stage D prostate cancer were eligible for study. Pain intensity ≥2 (see below) and significant increase in serum-acid phosphatase was required for patients with bone metastases as the sole metastatic parameter. Lack of cooperation, liver disease or adrenal insufficiency precluded participation in the trial.

Response of lymph node or lung metastases was defined according to the WHO criteria. A partial response of bone metastatic disease was defined as a reduction in pain intensity concomitant with a normalization in s-acid phosphatase and recalcification of osteolytic bone lesions and with no progression in osteosclerotic lesions. A complete bone response further required disappearance of pain and disappearance of tumor cells in repeated bone biopsies [4]. Performance status was scored according to the ECOG criteria [4]. Pain intensity was evaluated according to a scale from 0 to 3: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain.

Before initiation of treatment, the following examinations were performed: physical examination including blood pressure and rectal examination, chest X-ray, roentgenographic bone survey, bone scan and bilateral iliac crest bone biopsy. Abdominal CT scan was performed when indicated. Blood tests included: s-testosterone, *p*-cortisol, s-acid phosphatase, alkaline phosphatase, aspartate aminotransferase (ASAT), bilirubin, creatinine, electrolytes, calcium and phosphorus.

Physical examination including pain evaluation, chest X-ray and blood tests were repeated on day 3, 7, 14, 28 and thereafter every 4 weeks or when indicated. Concomitantly, *p*-ketoconazole was performed. Blood tests were taken within 2–4 h of ketoconazole intake. Roentgenographic bone survey, bone scan, abdominal CT scan and bone biopsies from the iliac crest were performed every 3 months.

Ketoconazole was given in a dosage of 400 mg p.o. every 8 h (200-mg tablets; Janssen Pharmaceutica, Beerse, Belgium). If s-testosterone was not reduced to castrate levels (<2.9 nmol/l = 1 ng/ml) [5] within 2 weeks or increased to above this level

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during the treatment, the dosage of ketoconazole was escalated to 400 mg every 6 h. Dose reduction to 300 mg every 8 h or eventually discontinuation of the treatment was indicated in cases with severe subjective side-effects. Discontinuation was also required in cases with severe adverse reactions or development of jaundice. A treatment duration minimum of 2 weeks was necessary for evaluation of response. Antacids or cimetidine were prohibited within 2 h of ketoconazole administration in order to secure sufficient gastric acidity for optimal drug absorption.

Increase in analgesic dosage was not allowed during the treatment if pain and bone metastases were the only evaluable parameters.

Patients were informed about the experimental nature of the treatment, and the investigation was approved by the local ethical committee according to the Helsinki Declaration.

Side-effects were graded from 0 to 3: 0 = no side-effects; 1 = mild but not really troublesome; 2 = troublesome; 3 = severe enough to discontinue the treatment.

A total of 20 patients were planned for the study. However, recruitment of patient was stopped after inclusion of 11 patients because of various serious side-effects.

RESULTS

Eleven patients were included in the study. All were evaluable for response. The median age was 68 years (range 43–78). Median performance status was 1 (range 0–3). Four patients had measurable retroperitoneal lymph node metastases on abdominal CT scan, one with additional neck node metastases and one with liver metastases. Three patients had groin or neck node metastases, two with additional bone metastases. The remaining four patients had bone metastases with increased s-acid phosphatase and bone pain as the sole evaluable response parameter. The characteristics of the individual patients are given in Table 1.

Effect on s-testosterone

Nine patients had a reduction in s-testosterone to castrate levels (<2.9 nmol/l) within 3 days of treatment start (Table 2). In the remaining two patients, an increase in the ketoconazole dose to 400 mg every 6 h did not lead to a sufficient reduction in s-testosterone. Subsequently, an additional five patients developed an increase in s-testosterone. In three of these, dose escalation was without effect in one and of minor and retarded effect in the other two patients (Table 2).

Response

Two patients had a complete response (one groin node and bone marrow and one retroperitoneal nodes (Fig. 1) and bone marrow) and four had a partial response (one neck node, one neck and retroperitoneal nodes, one retroperitoneal nodes (Fig. 2) and one bone) (Table 1), resulting in an overall objective response rate of 55% (6/11) (95% confidence limits: 23–83%). Additionally, two patients had significant bone pain relief without normalization of serum-acid phosphatase.

Effect on s-acid phosphatase

Eight patients had elevated s-acid phosphatase (Tables 1 and 3). In four patients normalization (≤10 U/l) occurred concomitantly with the clinical response. In one of these patients (no. 6), s-acid phosphatase subsequently increased at the time of relapse.

Effect on p-*cortisol*

In one patient (no. 9) *p*-cortisol transiently decreased to a subnormal level (56 nmol/l) immediately after initiation of ketoconazole treatment (normal: 100–700 nmol/l). In an additional patient (no. 6) *p*-cortisol decreased to a sustained subnormal level (22 nmol/l) after 12 months of treatment, but returned to normal levels after discontinuation of ketoconazole. Otherwise, *p*-cortisol stayed within normal limits.

p-*ketoconazole*

In patient no. 8 plasma levels of ketoconazole (Table 1) remained fairly low during the treatment even after dose escalation, probably explaining why this patient failed to obtain a sufficient reduction in s-testosterone (Table 2). However, patient nos. 5, 9 and 11 also had rather low *p*-ketoconazole levels but with excellent responses in s-testosterone (Table 2).

Adverse reactions and side-effects

Adverse reactions were prominent causing discontinuation of the treatment in nine patients (Table 4). Three patients developed hypertension (patient no. 10: 170/95 to 220/120; patient no. 7: 140/80 to 230/140; patient no. 4: 160/80 to 260/120). After discontinuation of ketoconazole, the blood pressure normalized. One patient developed a universal skin rash, while six patients experienced severe anorexia, nausea and emesis, one loosing 12 kg in weight. Five patients experienced mild and one patient moderate hot flashes. Two patients (nos 1 and 6) developed minor changes in liver function tests with transient increases in s-ASAT to 59 and 76 U/l, respectively (normal: 10–40 U/l) after dose escalation. Patient no. 10 had an initial and temporary drop in s-calcium to 1.04 mmol/l (normal: 1.30–1.50 mmol/l). No significant changes were seen in blood counts, s-bilirubin, creatinine, electrolytes and phosphorus.

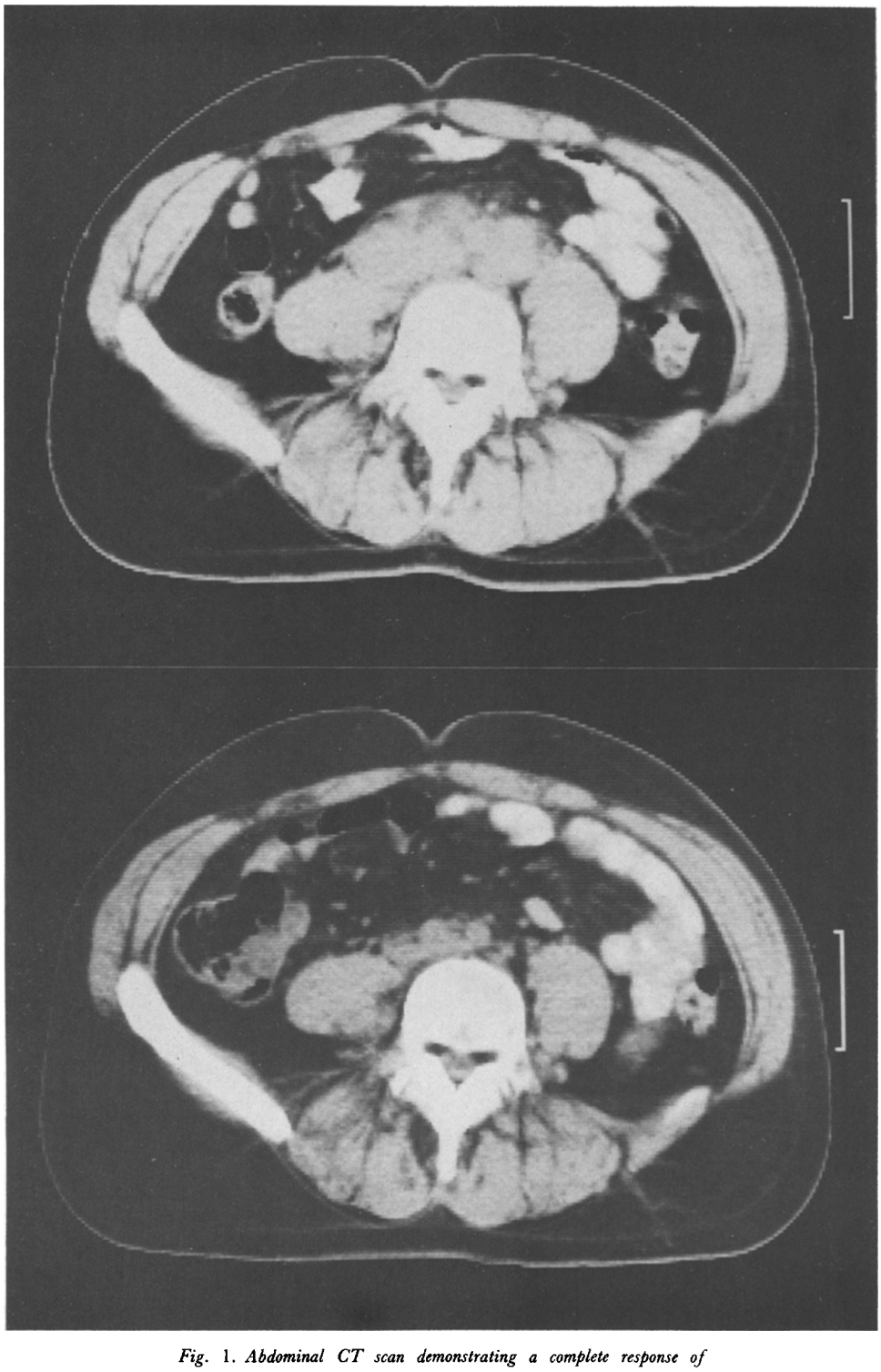

Fig. 1. *Abdominal CT scan demonstrating a complete response of retroperitoneal lymph node metastases to high-dose ketoconazole in a patient with prostate cancer* (*patient no.* 6).

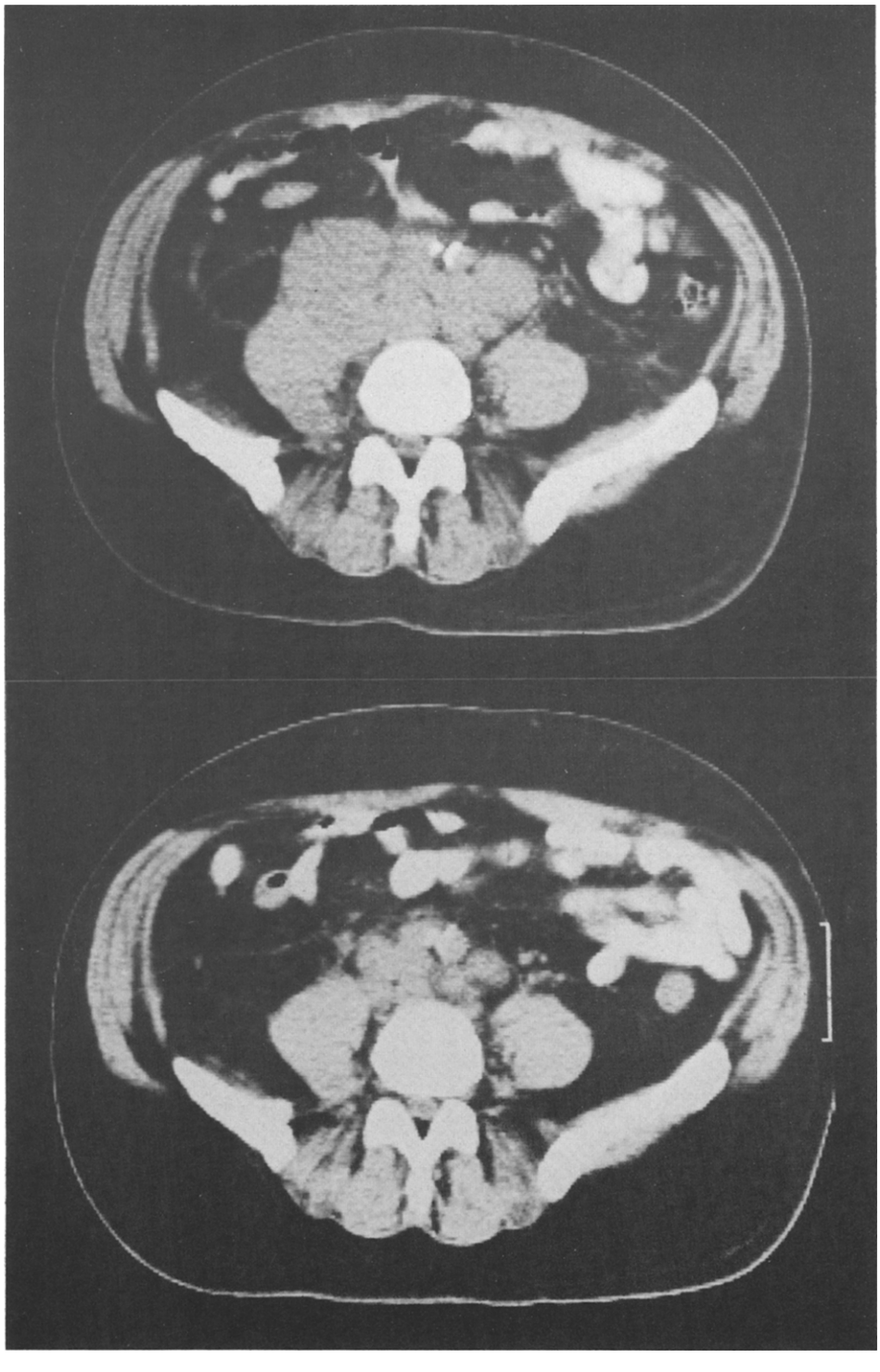

Fig. 2. Abdominal CT scan demonstrating a partial response of retroperitoneal lymph node metastases to high-dose ketoconazole in a patient with prostate cancer (patient no. 7).

Table 1. *Patients' characteristics, response to high-dose ketoconazole and* p-*ketoconazole levels*

Patient no.	Age (yr)	Performance status	Pain score	Metastases: Bone X-Ray	Bone Scan	Bone Biopsy	Lymph nodes Neck	Lymph nodes Groin	Lymph nodes Retroperitoneum (CT scan)	Acid phosphatase	Overall response	p-Ketoconazole median (μg/ml)*
1	72	1	0	n	+	n	+(PR)		Not done	n	PR(14 weeks)	13.1
2	60	2	3(→0)	+	+	+			Not done	↑		10.4
3	78	1	0	n	n	n		+	No parameter	n		9.6
4	62	0	2(→0)	+	+	+(CR)		+(CR)	Not done	↑ (→n)	CR(>16 weeks)	11.7
5	74	3	3(→0)	+	+	n			No parameter	↑ (→n)	PR(>8 weeks)	4.8
6	43	0	0	n	+	+(CR)			+(CR)	↑ (→n)	CR(36 weeks)	8.5
7	59	1	0	n	n	n			+(PR)	↑ (→n)	PR(11 weeks)	8.6
8	72	2	2	+	+	n			No parameter	↑		3.0
9	72	1	0	n	n	n	+(PR)		+(PR)	n	PR(>28 weeks)	4.6
10	56	1	2(→0)	+	+	+			No parameter	↑		6.6
11	68	2	2	+	+	+			+ Also liver	↑		4.9

n, Normal; CR, complete response; PR, partial response.
*Plasma ketoconazole was measured 2–4 h after drug intake.

Table 2. *Serum testosterone before and during high-dose ketoconazole treatment* (*normal*: 11–34 *nmol/l*; *castrate levels*: <2.9 *nmol/l*)

Patient no.	s-Testosterone (nmol/l) d0	d3	w1	w2	w4	w8	w12	w16	w20	w24	w28	w36	w48	w52
1	11.6	0.5	0.5	0.5	1.1	1.5*	0.8							
2	13.8	3.3	14.4	16.1*	15.0	6.7	9.9							
3	39.2	0.5	0.5	0.5	5.7									
4	16.5	0.5	0.5	0.9	4.9*	6.4	2.3	3.2						
5	11.5	2.3	—	1.6	0.5	0.5								
6	15.8	1.3	5.0	8.7*	4.4	3.0	3.2	2.4	2.2	4.7	2.7	3.8	4.0	0.8
7	23.5	1.2	1.8	—	4.5*	12.1								
8	22.5	3.9	5.0	7.8	15.1*	6.8								
9	12.5	0.9	0.5	0.5	0.5	0.5	0.5	0.5	1.6	2.8	0.5			
10	7.4	0.5	0.5	0.6	0.8	1.0	0.5	0.5	1.9	1.4				
11	14.5	1.0	1.3	3.2	4.7	1.8	3.7	3.3						

d, Day; w, week.
*Increase in ketoconazole dose.

DISCUSSION

The objective response rate obtained with ketoconazole as demonstrated in this study is comparable or even slightly higher than what has been reported in larger series of diethylstilbestrol or orchiectomy [6]. Two patients had a complete response in lymph node metastases and in bone biopsies (disappearance of tumor cells) concomitant with normalization in s-acid phosphatase. Neither the bone scan nor the osteoblastic lesions on bone roentgenograms normalized in patient no. 4, substantiating that remodelling of the bone structure as evaluated by bone scans and roentgenograms does not necessarily take place after a complete response has been obtained. This stresses the necessity of using bone biopsy as an indicator of complete response in patients with only bone metastatic disease [4].

With respect to the antineoplastic effect of high-dose ketoconazole in previously untreated stage D prostate cancer, only a few studies have been published [3, 7, 8]. Trachtenberg and Pont found reduction of pain in all 14 evaluable patients with bone metastatic disease [3]. Acid phosphatase normalized in 9/13 patients with elevated pretreatment levels. Neither a detailed evaluation of pain nor of bone roentgenograms were reported. Denis *et al.* found relief of pain and a 'significant' decrease in acid phosphatase in 3/7 patients [7]. In the study of Tapazoglou *et al.* 3/9 non-castrated patients had a partial remission [8]. However, half of these patients had undergone previous hormone therapy. No specification of the responding sites was given in this study.

A prompt reduction in s-testosterone was observed in the majority of our patients, but in two

Table 3. Serum acid phosphatase before and during ketoconazole treatment (normal: ≤10 U/l)

Patient no.	s-Acid phsophatase (U/l)													
	d0	d3	w1	w2	w4	w8	w12	w20	w24	w28	w36	w48	w52	
1	8	6	9	5	7	5	8							
2	49	48	30	44	36	22	19							
3	11	7	6	5	8									
4	128	80	23	38	29	14	14	9						
5	240	390	186	75	20	5								
6	382	345	47	38	17	8	10	8	8	10	9	17	98	120
7	43	9	7	6	4	7								
8	33	32	36	20	22	17								
9	10	8	10	20	15	21	20	16	13	14	14			
10	71	40	26	30	28	22	15	13	15	14				
11	47	27	30	17	25	16	25	22						

d, Day; w, week.

Table 4. Reasons for discontinuation of ketoconazole treatment and side-effects graded according to the ECOG criteria

Patient no.	Reasons for discontinuation		
	Progression	Side-effects	
1	+	+	nausea, fatigue 2
2	+	+	skin rash
3		+	nausea 3
4		+	anorexia, weight loss 3 hypertension 3
5		+	nausea, emesis 2–3
6	+(only bone)		
7	+	+	hypertension 3
8	+	+	anorexia, nausea 2–3
9		+	nausea, emesis 2–3
10	+	+	hypertension 3
11	+		

patients (18%) not even dose escalation to 400 mg every 6 h was sufficient to reduce s-testosterone to castrate levels. In addition, a rebound in s-testosterone to above castrate level was subsequently seen in five patients (45%), of whom three (27%) were refractory to increase in ketoconazole dose. This was observed despite excellent patient compliance and satisfactory *p*-ketoconazole levels. The reason for this subsequent rise in s-testosterone may be an increase in plasma gonadotropin levels (LH) secondary to the decrease in s-testosterone [3, 9].

Side-effects and adverse reactions were prominent, causing discontinuation of the treatment in 9 of the 11 patients. Subjectively, gastrointestinal upset was excessive in half of the patients. This incidence was higher than previously reported [3, 8]. Three patients developed severe hypertension during the treatment. This complication was thought to be due to the mineralocorticoid effect of an excessive increase in *p*-deoxycorticosterone [10].

A reduction in cortisol response to ACTH has been reported during high-dose ketoconazole treatment [11, 12]. Plasma cortisol was reduced to subnormal levels in two patients in our study. This is in contrast to Heyns *et al.*, who found all *p*-cortisol determinations within normal limits in nine patients receiving high-dose ketoconazole [9]. In four patients examined for plasma levels of 11-deoxycortisol, a pronounced increase was found [10]. Increases in deoxycorticosterone and 11-deoxycortisol indicate an inhibition of the cytochrome P-450-dependent adrenal 11β-hydroxylase [10, 13–16]. Another metabolic disturbance found during high-dose ketoconazole treatment was transient hypocalcemia probably due to interference of the drug with vitamin D [17]. Liver toxicity has been reported secondary to ketoconazole treatment [18]. In our study, mild transient increase in s-ASAT was observed in two patients after dose escalation, however, no cases of severe liver dysfunction were observed.

In contrast to castration, medical hormone manipulations including high-dose ketoconazole treatment require good compliance of these often elderly patients. Ketoconazole has to be taken strictly on a regular less than 8 h basis in order to keep testosterone production down. This, in connection with the many subjective side-effects, especially gastrointestinal upset, renders compliance difficult.

Side-effects, profound metabolic disturbances and rebound of s-testosterone make high-dose ketoconazole less atrractive as the sole therapy in stage D prostate cancer compared to conventional hormone manipulations. However, ketoconazole may find a place in combination with LHRH agonists during the first 2 weeks of therapy in which a paradox increase in s-testosterone may result in an acceleration of the disease causing 'flare' of symptoms [19, 20]. Another application of high-dose ketocon-

azole may be an initial short-term treatment in order to select patients who respond to hormonal manipulations and therefore should be candidates for castration.

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