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M.W. Köllermann[a]
K. Pantel[d]
Th. Enzmann[a]
U. Feek[b]
J. Köllermann[a]
M. Kossiwakis[a]
U. Kaulfuss[a]
W. Martell[a]
J. Spitz[c]

[a] Department of Urology,
[b] Institute of Pathology and
[c] Department of Nuclear Medicine,
Dr. Horst Schmidt Kliniken, Wiesbaden, and
[d] Institute of Immunology,
L.M. University of Munich, Germany

Supersensitive PSA-Monitored Neoadjuvant Hormone Treatment of Clinically Localized Prostate Cancer: Effects on Positive Margins, Tumor Detection and Epithelial Cells in Bone Marrow

Abstract

Objective: The present study was done to investigate the effects of supersensitive PSA-controlled inductive treatment on positive margins, detection of tumor and epithelial cells in bone marrow of 101 patients with untreated and clinically localized prostatic carcinoma (cT1–3N0M0). **Methods:** Hormonal treatment was given until PSA (DPD Immulite® third-generation assay) reached <0.1 ng/ml or the nadir value, as shown by two consecutive measurements at monthly intervals. **Results:** The resultant median duration of treatment was 6 months (range 3–22). Ninety-three (93%) of our patients reached a PSA value <0.1 ng/ml. The nadir of 6 patients (6%) was between 0.1 and 0.3 ng/ml, and it remained >0.3 ng/ml in only 1 case. Of the 101 patients, 82 had a measurable hypoic lesion on initial transrectal ultrasound. 84% of these became smaller, 7.5% remained unchanged and 8.5% increased. Of the 101 prostatectomy specimens, 20 (20%) were margin-positive. The incidence of affected margins was relatively high (35% from 55 patients) with cT3 tumors, but almost negligible (2% from 46 patients) in cT1–2 tumor. Our pathologists, despite their great experience in evaluating hormonally treated prostates (>500 cases) and using immunohistochemical staining, were unable to detect carcinoma in 15 (15%) specimens. Whereas only 2 (4%) of the 55 cT3 specimens were without detectable tumor, this incidence rised to 28% (13 of 46 prostates) in patients with cT1–2 tumors. Of the initial 29 patients with epithelial cells in bone marrow, only 4 (14%) remained positive after controlled induction and all of them had fewer cells than before. **Conclusion:** Endocrine induction controlled by a supersensitive PSA assay and continued until reaching PSA nadir is highly effective in clearing surgical margins and eliminating tumor cells from bone marrow. It seems to be clearly superior to the conventional 3 months of pretreatment at least in cT1–2 tumors in respect to surgical margins and detectability of tumor in the resected prostate. A definitive statement about the value of endocrine induction can only be given by prospective randomized studies, with optimal drugs, doses and treatment time. But the conventional 3 months of pretreatment are far from exploiting the possibilities of this therapeutic option.

Key Words
Localized prostate cancer
Neoadjuvant treatment
Affected margins
Detectability of tumor
Tumor cells in bone marrow

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Prof. M.W. Köllermann
Urologische Klinik, Städt. Klinikum
Ludwid Erhardstrasse 100
D–65199 Wiesbaden (Germany)
Tel. +49 611 432402/03, Fax +49 611 432124

Introduction

Radical prostatectomy cures clinically localized prostatic cancer if it succeeds in removing all malignant cells. Unfortunately, in many cases, the operation is performed too late to achieve this goal. As a consequence, local tumor rests and/or systemic micrometastases persist and may decide the fate of many patients. Positive margins point to local recurrence and epithelial cells in bone marrow to micrometastases. Of course they do not always imply the same end result. Nevertheless, it appears highly desirable to reduce the incidence of both. Whether this will result in better survival remains to be seen. However, prostatic carcinoma would be a very unusual tumor if it did not.

Several studies show that the incidence of positive margins can be reduced by 3 months of endocrine pretreatment. However, this rigid time schedule is arbitrary and does not take into account the many peculiarities of the disease. Among patients treated by intermittend androgen suppression, Goldenberg et al. [1] observed that PSA nadir and maximal soft tissue metastatic regression were not reached until 8 months in many patients. At the 1995 AUA meeting the same group [2] claimed: 'Maximal biochemical and pathological downstaging requires 8 months of neoadjuvant hormonal therapy prior to radical prostatectomy.' On the other side, in a more recent paper [3], these authors stated that among 50 patients with clinically confined prostate cancer treated for 8 months, 34% reached the PSA nadir at 3 months, 60% at 5 and 84% (not 100%) at 8 months. These data strongly suggest that the duration of inductive treatment should be individualized and not schematized to achieve maximal effectiveness and minimal costs.

In the present study, 101 patients with clinically localized prostate cancer were treated by complete androgen deprivation and monitored with a supersensitive PSA assay until PSA nadir or a value <0.1 ng/ml was reached, as shown by two consecutive PSA measurements at monthly intervals. We present the effects of this more individualized and controlled treatment on positive margins, detectability of tumor in the prostatectomy specimen and tumor cells in bone marrow.

Patients and Methods

One hundred and one patients with untreated and clinically localized prostatic carcinoma (cT1–3N0M0) were submitted to neoadjuvant complete androgen deprivation treatment. cT stage was determined by digital rectal examination (DRE). Laparoscopic lymphadenectomy and bone scans to exclude metastases were done if the initial PSA value exceeded 10 ng/ml. Additionally, all patients had a thorough transrectal ultrasonographic examination (TRUS) with measurement of the prostate and if possible also the 'tumor volume'. For the latter, the three major perpendicular diameters of eventual hypoechoic areas were measured and volume calculated according to the prolated ellipsoid formula. Furthermore, 86 patients had a bilateral, iliac bone marrow biopsy initially for detection of epithelial cells. Of these, 75 were rebiopsied at the time of radical prostatectomy. After these initial examinations and after obtaining informed consent, endocrine treatment with flutamide (Fugerel® 3 × 250 mg/day) and leuproreline acetate (Enantone® 3.75 mg monthly) was initiated and continued until the day before operation. Patients were controlled at roughly monthly intervals in a special prostate cancer clinic during endocrine treatment. At each visit, PSA, DRE and TRUS were repeated. If PSA did not fall on two consecutive, monthly examinations or was found to be <0.1 ng/ml twice, the nadir was considered to be reached and the patient submitted for radical prostatectomy.

PSA determinations were done by the DPD Immulite® third-generation assay with an analytical sensitivity of <0.003 ng/ml. For TRUS we used a 7.5-MHz multiplanar probe (Kraetz®). Epithelial cells in bone marrow were detected by immunochemistry using the monoclonal antibody CK2, to epithelial cytokeratin component 18 (CK18). Technical details have been published elsewhere [4]. Radical prostatectomy was done in the majority of patients by the transcoccygeal route. Specimens were inked, then fixed in formalin 10% and cut in 3-mm-thick blocks, according to the Stanford protocol. Routine histopathology was done on HE-stained slides. Additional immunohistochemical staining with antibodies to high molecular cytokeratin (M903) and pancytokeratin (Lu 5) were carried out in every case if no tumor was detected on routine examination and if HE was considered insufficient concerning infiltration of the margins.

Results

Patient Characteristics. Forty-six patients had a clinical T1 (25) or T2 (21) tumor and 55 were cT3 cases. Only 82 (82%) had measurable hypoechoic lesions on TRUS. They were smaller in cT1–2 (0.2–3.3, median 0.77 ml) than in cT3 cases (0.14–10.7, median 1.39 ml). The median of initial PSA was 12.85 ng/ml (range 0.5–208). As expected, it was higher in cT3 tumors (14.7) than in lower stages (11.2). Clinical T1+2 tumors were on the whole (72%) well differentiated (≤G2a). On the contrary, cT3 cases were predominantly (73%) high-graded (≥G2b). Eighty-six of the 101 patients had a pretherapeutic bone marrow biopsy. Epithelial cells were found in 29 (34%). This was more frequent (43%) in cT3 than in cT1–2 cancers (24%), in patients with hypoechoic lesions over 2 ml (50%) than with smaller foci (29%), and with high-grade (32%) than low-grade tumors (26%).

Duration of Treatment. Median duration of controlled, inductive treatment was 6 months and it varied between

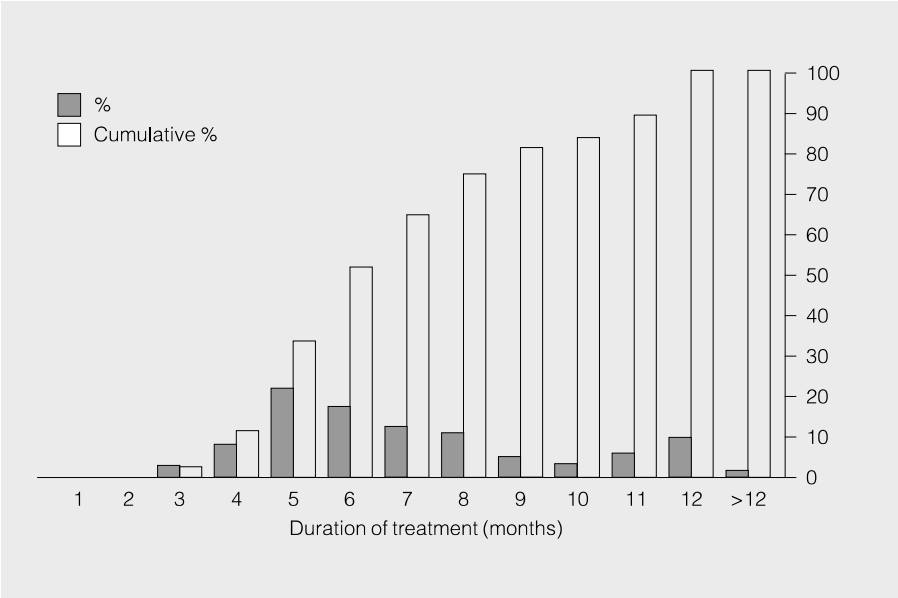

Fig. 1. Duration of treatment (see text for details).

Table 1. Margins of 101 prostatectomy specimens after controlled induction in relation to the initial cT stage

cT stage	Margin-positive	Margin-negative	Total
T1+T2	1 = 2%	45 = 98%	46 = 100%
T3	19 = 35%	36 = 65%	55 = 100%
T1+T2+T3	20 = 20%	81 = 80%	101 = 100%

Table 2. Frequency of no tumor detectable (pT0) in 101 prostatectomy specimens after controlled induction, in relation to the initial cT stage

cT stage	Patients	No tumor detectable (pT0)	
		n	%
T1+T2	46	13	28
T3	55	2	4
T1+T2+T3	101	15	15

3 and 22 months. After 3 months only 3% of our patients reached the PSA nadir, and even at 8 months 25% did not (fig. 1). There was no significant difference in treatment time beween cT1+2 vs. cT3, high-grade vs. low-grade tumors and patients with hypoechoic lesions >2 ml vs. <2 ml.

Effect on PSA. Ninety-three (93%) of our 101 patients reached a PSA nadir of 0.1 ng/ml or below. The nadir of the remaining patients was between 0.1 and 0.3 ng/ml in 7 (7%) and over 0.3 ng/ml in 1 (1%).

Effect on Hypoechoic Lesions. Of the measurable hypoechoic lesions in 82 patients, 69 (84%) became smaller, 6 (7.5%) remained unchanged and 7 (8.5%) increased. Whereas the median initial volume of hypoechoic lesions was 1.13 ml after induction it was 0.46 ml.

Effect on Epithelial Cells in Bone Marrow. Of the 29 patients with epithelial cells in bone marrow before inductive treatment, only 4 (14%) remained positive thereafter, and all of these 4 patients had fewer cells than initially.

Effect on Specimen Margins. Of our 101 patients, 20 (20%) had positive and 80 (80%) negative margins (table 1). The rate of negative margins was extremely low in the group of 46 patients with clinical T1 and T2 tumors (2%) in comparison to the 55 T3 cases (35%).

Effect on Tumor Detection. In 15 (15%) of the 101 prostatectomy specimens, the pathologist was unable to detect carcinoma (table 2). This was rare in cT3 cases (2 = 4%) but surprisingly frequent with cT1+2 tumors (13 = 28%).

Discussion

Duration of Treatment

Inductive treatment of prostatic carcinoma was inaugurated by Vallet [5] in 1944. Since then, the proposed duration and means of hormonal manipulation has varied widely. The majority [6–12] of recent studies referred to 3 months of pretreatment. On the other hand, already some of the pioneers of neoadjuvant therapy administered a more individualized and prolonged schedule. In 1949, Parlow and Scott [13] pretreated their patients during 3, 4, 6, 12, 15, 24 and 36 months respectively, monitoring response by DRE. Recently the Vancouver group [1–3] argued again in favor of a more prolonged induction, but they also used a prefixed time schedule of 8 months. Their results on margins were clearly better than the data reported from 3-month series. The present study confirms the general superiority of a longer treatment, but it shows on the one hand that not all patients need 8 months, and on the other that a few must be treated considerably longer.

Effect on PSA

PSA has been shown to be a very sensitive tool for evaluation of primary treatment in patients with prostatic carcinoma. The tumor is responding as long as PSA is falling and progressing when it rises [14]. However, progression may also (very seldom) occur without an increasing PSA. All of our patients showed a decrease in serum PSA after the beginning of neoadjuvant hormonal therapy. Thus, all of them were responders. But the response shown by declining PSA values may be due to downregulation of PSA expression and shrinking of PSA-producing tissues (specially normal prostate and prostatic carcinoma). The primary goal of neoadjuvant treatment is however reduction of tumor mass to enhance the chance of eradication by radical prostatectomy. In view of the different reasons why PSA decreases under endocrine treatment, it is not surprising that the decline of PSA is not proportional to the reduction of tumor burden. Gleave et al. [3] called attention to the biphasic slope of PSA decrease: a precipitous fall specially during the first, but also during the second and third month and a much more gradual, subsequent decrease until the nadir is reached. It is tempting to speculate that phase one is predominantly due to downregulation of PSA expression, whereas during the second phase, mass reduction of PSA-producing tissues prevails. The assumption that tumor shrinking at least continues after first phase PSA decline is supported by the effects of prolonged treatment on prostatectomy specimens (margins and tumor detectability).

The analytical sensitivity of commonly available PSA assays limits their usefulness as indicators of response precisely where they are most needed: in the second phase of the slope or <0.3 ng/ml. In recent years however, several PSA assays with lower analytical detection limits have been developed. In the present study the DPD Immulite® third-generation PSA assay was employed. It claims an analytical detection limit of <0.003 ng/ml and a working range of 0.01–20 ng/ml [15]. With a test of this sensitivity the slope of declining PSA can be followed far beyond the limits of conventional assays. We arbitrarily chose <0.1 ng/ml as an endpoint of pretreatment. However, probably for many patients this was not the real endpoint of the PSA slope. Whether continuation of treatment to the absolute nadir is worthwhile has yet to be shown. Our results suggest that this indeed may be the case, at least for patients with cT3 tumors.

Effect on Hypoechoic Lesions

Carcinomatous lesions of the prostate are predominantly hypoechoic. Despite the fact the many other entities are also hypoechoic, serial measuring of them may contribute more specific information about shrinking of tumors. The fact that the great majority (84%) of hypoechoic lesions became smaller by more than 50% gives additional support to the thesis that the lowering of PSA is not only caused by downregulation of PSA expression or downsizing of the normal prostate, but also by a real and considerable reduction of the tumor mass itself. This confirms data published by Pinault et al. [16] in a smaller series.

Effect on Epithelial Cells in Bone Marrow

Extrinsic cells in bone marrow detected by immunostaining with anticytokeratin antibodies are supposed to be tumor cells. This assumption is supported by the following observations: (1) These cells are almost exclusively found in patients with epithelial tumors and not in patients without cancer [17]. (2) In patients with prostatic carcinoma, cytokeratin-positive cells in bone marrow carry the same chromosomal abnormalities (aneusomies) as the primary tumor [18]. (3) In prostatic cancer patients these cells may express PSA and PSMA epitopes [19]. (4) Cytokeratin-positive cells in bone marrow show several tumor-associated characteristics such as increased expression of oncogenes, downregulation of MHC antigens, growth in cell culture and SCI mice [20–22]. (5) The detection of epithelial cells in bone marrow is of prognostic significance in patients with various types of solid epithelial tumors [23, 24, 28]. This, however, has not been

Table 3. Frequency of positive margins in untreated und conventionally pretreated patients with clinically localized prostatic carcinoma

Authors	Untreated		Pretreated	
	patients	margin +, %	patients	margin +, %
Fair et al. [6]	92	36	92	11
Pedersen et al. [7]	54	46	60	24
Soloway et al. [8]	137	47	144	17
Labrie et al. [9]	71	34	90	8
Klotz et al. [10]	91	65	101	28
Bellavance et al. [11]	275	39	165	24
Debruyne et al. [12]	154	44	136	26
Van Poppel et al. [36]	62	46	65	32
Total/average	936	45	853	21

Table 4. Margin positivity after conventional pretreatment of patients with cT1–2 tumors in comparison with our results after controlled induction

Authors	cT stage	Patients	Margin +, %
Soloway et al. [8]	2b	144	17
Klotz et al. [10]	1–2	101	28
Bellavance et al. [11]	1–2	165	24
Debruyne et al. [12]	2	68	13
Fair et al. [6]	1–2	111	11
Van Poppel et al. [36]	2	36	19
Labrie et al. [9]	1–2	75	8
Total/average		700	17
Ipse	1–2	46	2

Table 5. Margin positivity after more prolonged and controlled pretreatment of patients with cT1–2 tumors

Authors	cT stage	Patients	Margin +, %
Bellavance et al. [11]	?	40	6
Gleave et al. [3]	T1–2	44	4
Ipse	T1–2	46	2

Table 6. Margin positivity after conventional pretreatment of patients with cT3 tumors in comparison with our results after controlled induction

Author	cT stage	Patients	Margin +, %
Gomella et al. [32]	cT3	21	43
Debruyne et al. [12]	cT3	61	44
Fair et al. [6]	cT3	27	26
Abbas et al. [33]	cT3	8	25
Solomon et al. [34]	cT3	8	37
Cher et al. [35]	cT3	26	31
Van Poppel et al. [36]			
Labrie et al. [9]	cT3	15	6
Total/average		195	33
Ipse	cT3	55	35

clearly demonstrated for patients with prostatic carcinoma.

The results of the present study, which found epithelial cells to be more frequent in bone marrow of patients with large and undifferentiated than with small and well-differentiated cancers, reinforce the concept of their tumorous nature. It is also supported by their marked reduction after neoadjuvant therapy. But all this does not mean that the finding of these cells in bone marrow of patients with seemingly localized prostatic carcinoma is tantamount to the presence of micrometastases, which sooner or later grow up to overt filiae. At least some of them may disappear by mechanisms of self-defense or lack of vitality. This is supported by the following facts: (1) Using PSA RT-PCR in bone marrow, Melchior et al. [25] found a positive reaction in 62% of 69 patients with clinically localized prostatic cancer. This is an incidence well above the reported relapse rates. (2) The same group performed bone marrow rebiopsies on 24 formerly positive patients after radical prostatectomy. Only 6 (25%) had a persistently positive RT-PCR.

All we know is that tumor cells are an absolute prerequisite for the development of metastases. But how often

this occurs and if the risk of it is reliably reduced by eliminating or diminishing them is open to question and must be further investigated. At least one of the criticisms of neoadjuvant treatment, namely that the tumor may metastasize in the meantime, seems highly improbable in view of our results.

Effects on Specimen Margins

Positive surgical margins are associated with an increased risk of relapse [26]. Their incidence in patients without pretreatment varies from 16 to 65% [27]. Reducing margin positivity may therefore improve the results of radical prostatectomy. Various studies showed that endocrine treatment is able to decrease the frequency of affected margins (table 3). Drugs and doses employed by these authors varied, but all of them (except Bellavance et al. [11] who used a more prolonged pretreatment for some of their patients) used a rigid time schedule of approximately 3 months (van Poppel et al. [36], 6 weeks). Comparing their results with ours (table 1) shows: the overall incidence of positive margins is almost the same (21 vs. 20%), suggesting no difference between treatment modalities. But this is easily explained by patient selection. Whereas the vast majority (88%) of the patients compiled in table 3 had cT1–2 tumors, only 46% of ours belonged to this category. The remaining majority of 54% were cT3 cases. In table 4 we extracted the cT1–2 patients from table 3 (where this was possible). Comparing now the results of standard pretreatment in cT1–2 tumors with ours of the same stage shows a clear advantage of controlled induction: 17 vs. 2% positive margins. This very low incidence of margin positivity in our admittedly small series of cT1–2 tumors is confirmed by the results of others, who also employed longer pretreatment times (table 5).

Comparing however the results of standard pretreatment in cT3 cases with ours of the same stage shows no advantage of controlled induction: 33 vs. 35% positive margins (table 6). But considering on the one hand the very small number of cases in the majority of the series compiled in table 6, with widely diverging results and the even smaller amount of data from more prolonged treatment schedules on the other, it seems too early for final conclusions. This item clearly deserves further studies.

Effect on Tumor Detection

The most surprising result of the present study was that after controlled induction, 28% of our patients with initial cT1–2 tumors had no tumor detected in their prostatectomy specimen. In patients with cT3 tumors the incidence was only 4%. This is not new. It was first reported by Gutierrez [28], one of the pioneers of inductive treatment, in 1949. Thereafter, many additional cases were more or less casually mentioned in multiple publications.

There are various reasons why an initially diagnosed carcinoma may be missed in the resected prostate after inductive treatment: (1) The initial carcinoma was very small and despite its unaltered persistence it is simply overlooked. (2) The tumor suffered marked regressive changes and cannot be identified despite its persistence. (3) The tumor was really eliminated by inductive treatment. We believe that none of these reasons is explicatory to all of our cases, but all of them may be contributory.

Conclusions

Biochemical relapse occurs in 35–40% of the patients submitted to radical prostatectomy for a seemingly resectable carcinoma. This rather high failure rate is due to carcinomatous cells left behind locally and/or elsewhere. Positive margins and epithelial cells in bone marrow are suspected to be forerunners of relapse. A series of prospective and randomized studies showed that margin positivity can be reduced by endocrine pretreatment of 6–12 weeks' duration. Nevertheless, at 2 and 3 years the recurrence rate could not be improved with these regimens [29–31]. Recently a few studies [1–3, 11] presented evidence that longer pretreatment (e.g. 8 months) is more effective on margins than conventional schedules. This is roughly confirmed by the present study at least in T1–2 cases. In addition, we found a surprisingly high rate of no tumors detected in our prostatectomy specimens and a marked reduction of epithelial cells in bone marrow. In view of these results we are convinced that the conventional 3 months of pretreatment do not exploit the possibilities inherent to neoadjuvant hormonal therapy, at least in the majority of patients. As with any other therapy, a meaningful evaluation presupposes adequate treatment times. Our data suggest that this cannot and in consequence should not be fixed ad hoc for all patients and tumors, rather it must be individually searched for by PSA monitoring with an assay of high sensitivity.

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