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ORIGINAL PAPER

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Intermittent androgen deprivation in advanced prostate cancer

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The incidence of prostate cancer shows a rising incidence not only in the United States but also in the European Community. Peak incidence occurs at the age of 70 years, and it accounts for approximately 15% of all male cancers [23]. The majority of all male patients who have presented in the past several years have had locally advanced or metastatic prostate cancer. Perhaps, the increasing awareness of the male population and the introduction of prostate-specific antigen (PSA) determination in combination with digital rectal examination (DRE) in the workup of patients with lower urinary tract symptoms (LUTS) will lead in the near future to a decrease in the number of patients with advanced prostate cancer [15, 19, 29]. In the United States a trend has already been observed of the detection of earlier stages of prostate cancer due to the institution of the so-called Prostate Cancer Awareness Weeks [7, 10]. Standard treatment for patients with advanced prostate cancer is based on androgen deprivation, which can be achieved in different ways (Table 1).

Based on prognostic factors such as tumor stage, tumor volume, alkaline phosphatase, histologic grade, performance status, presence of pain and level of tumor markers (PSA), the timing and extent of androgen deprivation (monotherapy or combined androgen blockade) can be adopted [32, 35]. In 40–85% of cases hormonal therapy will result in a subjective and/or objective remission, depending on the presence of the aforementioned prognostic factors [11, 18, 25]. However, hormonal deprivation is not a curative therapy and within 2 years 80% of patients will eventually relapse [6]. Hormonal escape can be explained because prostate cancer consists of hormone-dependent and hormone-sensitive cells (which will determine the response on androgen withdrawal) and hormone-independent cells (which continue their natural growth after androgen withdrawal) [8].

Because hormonal therapy in advanced prostate cancer does not result in cure, but can influence considerably the quality of life through its induced side effects (flushes, erectile dysfunction, gynecomastia, gastrointestinal effects, loss of energy, etc.), modifications of hormonal therapy have been investigated, such as delay of active treatment until symptomatic disease occurs or so-called intermittent androgen deprivation.

In the following paragraphs the available scientific background, animal studies and clinical studies applying intermittent androgen deprivation therapy in prostate cancer are discussed.

Background

Androgens play an important role in the initiation of DNA synthesis, cell proliferation and apoptosis (controlled cell death) at the cellular level of the prostate eliminating prostate cells during androgen suppression, mediated directly or indirectly by unligated androgen receptors. The most important source of androgen production stems from the testes and from the adrenal cortex. After the release of luteinizing hormone (LH), testosterone is released and converted in the prostate cell nucleus by 5 α -reductase into the active form of dihydrotestosterone (DHT). The DHT binds preferentially to the androgen receptor and subsequently this complex associates with the nucleotide recognition sequences on the genome. The adrenal cortex is regulated by the production of adrenocorticotrophic hormone (ACTH) and this elicits the production of androstenedione, which can be converted again to testosterone. The interaction of DHT with the nuclear androgen receptor allows the regulation of the transcription of specific genes, resulting in the production of proteins and growth factors [14]. All of the above-mentioned treatment modalities of androgen deprivation interfere with this hypothalamic-adrenal-gonadal axis. The explanation for the hormonal escape has been studied by many investigators. Bruchovsky et al. [5] found in the Shionogi mouse mammary androgen-dependent carcinoma that androgen withdrawal resulted in an adapta-

Table 1 Methods of androgen deprivation in advanced prostate cancer

Orchiectomy	+ total + subcapsular + subepididymal
LHRH analogues	+ daily s.c. + 1, 2, or 3 monthly s.c./i.m.
Antiandrogens	+ steroidal + nonsteroidal
Combined androgen blockade	

tion of androgen-dependent stem cells in the tumor cell population; in the case of tumor progression and/or recurrent tumor growth a 20-fold increase in the proportion of total stem cells was observed and a 500-fold increase in the proportion of androgen-independent stem cells. A second explanation could be a mutation in the hormone-binding domain of the androgen receptor, which is not uncommon after androgen withdrawal and which may thus provide a selective growth advantage [33, 34]. The recently reported "androgen withdrawal syndrome" resulting in a PSA decline and/or clinical improvement in 30–40% of patients after stopping flutamide therapy (but also observed after the cessation of bicalutamide, diethylstilbestrol and megestrol acetate) could be an explanation for this phenomenon [4, 9, 28, 30, 31]. Also, mutations in the tumor suppressor gene p53 and the proto-oncogene *bcl-2* have been observed after androgen deprivation [21].

These observations have led to the assumption that intermittent androgen deprivation could possibly temporarily prevent or inhibit the transition to an androgen-independent state of the prostate tumor cells, because gene mutation and/or an increase in androgen-independent stem cells were prevented.

Animal studies

The effects of intermittent androgen deprivation on prostate tumor growth, gene expression and apoptosis have been investigated in different tumor models. Akakura et al. [1] observed in the Shionogi tumor model that the time to an androgen-independent tumor growth was threefold longer than continuous androgen deprivation (147 vs 51 days).

In the LNCaP tumor model (a human, androgen-dependent prostate tumor) intermittent androgen deprivation was studied in order to delay the development of androgen-independent regulation of the PSA gene [12]. In this tumor model serum PSA correlates with tumor volume and a significant decrease in serum PSA is observed approximately 7 days after castration. After continuous androgen deprivation, an adaptation to an androgen-depleted environment is seen from day 24 on. A threefold prolongation in time to androgen independence was seen using the intermittent androgen deprivation regimen (75 vs 24 days). PSA levels increased 2- to 5-fold by 60 days post-castration in the control group,

compared to only 0.5-fold in the intermittently treated group.

However, time to progression defined by PSA and tumor growth in 20 athymic mice with LuCaP 23.12 prostate cancer (an androgen-sensitive prostate tumor) was not different compared to control mice treated with castration [27]. In the R-3327 rat prostatic carcinoma (well-differentiated, androgen-sensitive adenocarcinoma), rats on intermittently administered doses of diethylstilbestrol in drinking water (1 week on DES and 3 weeks off DES) showed no survival benefit compared to control rats, although mean tumor volume was lower. Compared to castration, intermittent DES administration was inferior in this tumor model [26]. From these animal studies it can be concluded that the concept of intermittent androgen deprivation has a beneficial effect in the androgen-dependent tumor and this could not be shown in the androgen-sensitive tumor models.

Clinical studies

In 1986 Klotz et al. [16] described the first clinical experience using the concept of intermittent androgen deprivation in a pilot study. Twenty patients with different prognostic parameters were intermittently treated with diethylstilbestrol ($n = 19$) and flutamide ($n = 1$) (Table 2). Treatment was withheld if clinical response was observed and restarted in the case of symptomatic progression. The duration of hormonal therapy prior to cessation lasted a median of 10 months (ranges 2–70 months) and median time off therapy to first evidence of progression was 8 months (ranges 1–24 months) (Table 3). The authors concluded that satisfactory palliation could be achieved using this treatment scheme. However, this was based only on clinical impression and no questionnaires were used to substantiate this.

Recently, this concept was re-introduced in clinical practice and Goldenberg et al. [13] described a nonrandomized series of 47 patients who were followed during intermittent androgen deprivation. As shown in Table 4 these 47 patients had different clinical stages, ranging from localized to metastatic disease. All patients were treated for at least 6 months with a combined androgen blockade using cyproterone acetate with diethylstilbestrol or a luteinizing hormone releasing hormone (LHRH) analogue plus an antiandrogen. Patients were

Table 2 Tumor characteristics of 20 patients on intermittent hormonal deprivation therapy [16]

Stage	No. (patients)
B1-3	7
C	5
D1-2	8
Grade	
G1	3
G2	12
G3	4
Gx	1

Table 3 Duration of hormonal treatment prior to cessation and duration of withholding hormonal therapy, $n = 20$ [16]

Duration of hormone therapy (months)	No. Patients (prior stop) hormone therapy	No. patients (off hormone therapy)
2-3	4	4
4-6	4	1
7-12	3	4
13-24	6	3
>24	3	8

Table 4 Tumor characteristics, $n = 47$ [13]

Stage	No. patients
A2, B2	4
C	19
D1, D2	24

eligible if a serum PSA ≤ 4 ng/ml between 24 and 32 weeks was achieved. Combined androgen blockade was restarted if serum PSA levels increased to a mean value between 10 and 20 ng/ml. Subsequent cycles (= time on hormonal therapy + time off hormonal therapy) were given using this same regimen until the PSA regulation became androgen independent.

The mean time to achieve a PSA nadir was 20 weeks in cycle 1 and 18 weeks in cycle 2. After stopping androgen deprivation, testosterone levels returned to the normal range within 8 weeks (range 1-26 weeks). In the first cycle 30 patients were evaluated and the mean time off therapy was 30 weeks (range 9-108 weeks) and in the second cycle, based on 15 patients, the mean time off therapy was 33 weeks (range 17-87 weeks) (Table 5). In this small group of patients the prognostic factors, tumor stage and grade were not statistically significant different regarding treatment results. However, a large difference was found in patients not reaching a PSA nadir before a treatment period of 24-32 weeks concerning median survival time, and it was concluded that these patients in future trials should be excluded from an intermittent treatment protocol.

In both the aforementioned studies the effect of intermittent androgen deprivation on time to progression, survival, costs or impact on quality of life was not analyzed. Concerning the quality of life aspects, which were not evaluated with questionnaires, an improvement in the general well-being and recovery of potency in previously potent men was observed in the Goldenberg study. Bales et al. [2] evaluated the quality of life aspects

in 32 men on intermittent androgen deprivation using questionnaires. Twenty-four men returned the surveys; 60% reported a disappearance of hot flushes, 75% had a stronger sex drive and 62% reported an improvement of their erectile function when off hormonal therapy. However, a remarkable finding was that only 37.5% of men reported an improvement in overall well-being.

Discussion

The concept of intermittent androgen deprivation is based on experimental studies in different animal models and was tested in only small series of patients. The interpretation of these clinical studies is difficult due to the fact that a heterogeneous group of patients was included with different prognostic factors. It is therefore necessary to initiate trials with well-defined inclusion and exclusion criteria. The South West Oncology Group initiated a randomized trial comparing continuous with intermittent androgen deprivation in patients with stage D2 prostate cancer (SWOG 9346), and the EORTC-GU Group recently started a feasibility study in patients with metastatic prostate cancer (EORTC 30954). The EORTC started a feasibility study, because it was decided that the clinical data were too scarce to initiate a phase III study. Two other trials testing the intermittent androgen deprivation concept have been initiated in Canada (N. Bruchovsky) and Portugal (F. Calais da Silva), but in these two studies patients with nonmetastatic disease can also be included. Comparing the four studies with regard to criteria for stopping and restarting hormonal androgen deprivation, different rules have been defined. This is due to the fact that from the available data it is not clear when to stop hormonal deprivation and when to restart. This will probably impede final comparison of different studies. It is obvious that patients selected for this kind of study should be treated with a combined androgen blockade to prevent the so-called flare phenomenon and monthly depot preparations of the LHRH analogue. From the publication of Goldenberg et al. the conclusion can be drawn that patients probably should not be treated who do not reach a PSA nadir within 8 months. It is, however, unclear whether we should treat patients with androgen deprivation during a fixed period of time (6 months?) or whether androgen deprivation can be stopped if a "stable" serum PSA level has been reached. Even more difficult is the question of when to restart: above a PSA level of 10 ng/ml (Hybritech) or should a percentage serum PSA increase be considered? Conflicting reports have been published concerning a correlation between PSA decline and impact on time to progression and survival [20, 22, 24]. Besides, serum PSA levels can be influenced by different factors and changes in serum levels could be independent of tumor response [17]. These facts could weaken the use of serum PSA as a parameter to stop and restart hormonal deprivation therapy. Perhaps in the near future other more biological tools will become available, such as the ratio of free/total PSA or the reverse transcriptase-polymerase chain

Table 5 Duration of hormonal treatment prior to cessation and duration of withholding hormonal therapy, $n = 47$ [13]

Mean length of cycle	Mean time off combined androgen blockade (%)
First cycle ($n = 30$ patients): 73 weeks	30 weeks (41)
Second cycle ($n = 15$ patients): 75 weeks	33 weeks (45)

reaction-PSA, a test that is very sensitive in detecting circulating tumor cells [3].

In conclusion, intermittent androgen deprivation therapy should be considered as an investigational treatment modality and therefore patients should only be treated within the frame of a well-designed clinical trial. Evaluation parameters should not only be the time the patient is on and off androgen deprivation, time to progression and survival, but should also include quality of life aspects and costs of this treatment concept. The regular determination of serum PSA and the uncertainty for the patient about whether he can stop or whether he should restart hormonal treatment could have a considerable impact on cost and quality of life.

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