Etoricoxib and Intermittent Androgen Deprivation Therapy in Patients with Biochemical Progression After Radical Prostatectomy

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OBJECTIVES
To verify whether in patients with biochemical progression after radical prostatectomy (RRP), the administration of a cyclooxygenase-2 (COX-2) inhibitor during the off-phases of intermittent androgen deprivation (IAD) may increase the effectiveness and off-therapy time of intermittent therapy.

METHODS
This is a comparative, prospective study. A total of 44 patients with biochemical progression after RRP were included in a clinical protocol for IAD once prostate-specific antigen (PSA) levels progressed over 0.4 ng/mL. The 44 cases were randomly assigned to receive two different treatment strategies: group A received IAD therapy using bicalutamide 150 mg once daily in the on-phases and no therapy in the off-phases; group B received IAD therapy using bicalutamide 150 mg once daily in the on-phases and etoricoxib 60 mg once daily in the off-phases.

RESULTS
Median follow-up was 62 weeks. In group A of 22 (22.7%) cases and in group B of 22 (9.1%) cases failed to respond to IAD ($P < 0.05$). Comparing the two groups, in all three cycles of IAD the time of the cycles and the time of the off-phases were significantly ($P < 0.0001$) longer in group B than in group A. The highest PSA value reached during the off-phases in each cycle was significantly ($P < 0.001$) lower in group B than in group A. Withdrawal from treatment owing to side effects was not necessary in any of the 44 patients.

CONCLUSIONS
In patients with biochemical progression after RRP, we showed that the use of a COX-2 inhibitor in the off-phases of IAD is able to increase the off-treatment time significantly.

The effect of intermittent androgen deprivation (IAD) in prostate adenocarcinoma has been tested in cell lines and in humans. Kurek et al. and Tunn et al. suggested that IAD may also be an attractive option for the treatment of men with nonmetastatic prostate cancer who show a prostate-specific antigen (PSA) progression after radical prostatectomy (RRP).

Inflammation has been linked with the risk for several malignancies and also for prostate cancer. Cyclooxygenase-2 (COX-2) is a proinflammatory and inducible enzyme which can be induced by cytokines and growth factors in different cell types. Several studies have demonstrated the expression of COX-2 mRNA in human prostate tissue, in particular with 94% in the peripheral zone of the prostate. Several authors underlined a possible role of COX-2 in the progression of human prostate cancer. Moreover, analysis on prostate cancer cell lines verified a decreased cell proliferative index associated with the exposition to a COX-2 inhibitor. In human prostate tissue we immunohistochemically showed that the association of a COX-2 inhibitor significantly increases the cell apoptotic index in patients treated with a 5-alpha reductase inhibitor (finasteride). Smith et al. showed that in men with recurrent prostate cancer after RRP or radiotherapy, celecoxib compared with placebo significantly decreased mean PSA velocity and tended to increase the proportion of men who doubled their PSA double time.

In patients submitted to IAD, the off-phase represents a period in which prostate cancer is not treated. Considering the role of inflammation and COX-2 in prostate cancer control, the aim of this study is to verify whether the administration of a COX-2 inhibitor during the off-phases of IAD may increase the effectiveness, delay progression, and in particular increase off-therapy duration of IAD therapy. This concept may be particularly significant in cases with only biochemical progression of prostate cancer. Larger studies could analyse our hypothesis in terms of progression-free survival.
In both groups the initial treatment period (cycle 1, on-phase) included bicalutamide 150 mg once a day in the off-phases and etoricoxib 60 mg once a day in the off-phases. IAD therapy using bicalutamide 150 mg once a day in the off-phases lasted 12 weeks in all cases. After this period an acceptable nadir was considered to be a serum PSA level of less than 0.4 ng/mL and stable or decreasing. Bicalutamide therapy was then withheld until serum PSA increased to a value of 1.0 ng/mL or greater (off-treatment phase). The subsequent on-treatment phases lasted for the time needed to again reach the PSA level less than 0.4 ng/mL with a stable or decreasing value. The length of one treatment cycle was defined as the number of weeks under on-phase followed by the number of weeks under off-phase.

Either in group A or B, during the on-phases, all patients were submitted to bicalutamide 150 mg for daily therapy. In the off-phases, patients randomized into group A received no treatments whereas patients in group B received etoricoxib 60 mg daily.

Patients were seen at follow-up every 4 weeks during the treatment cycles. Treatment-related side effects and laboratory tests were determined at each follow-up examination. Treatment was discontinued early for any participants with an expected serious adverse event or with progressive disease.

In each cycle, serum PSA levels were measured every 4 weeks. Either in group A or B, during the on-phases, time of on-phases, highest PSA reached during the off-phases, and time of each cycle. IAD was considered to have failed when a patient was no longer able to cycle off-treatment (PSA did not reach a level less than 0.4 ng/mL during on-phases). These examinations were negative in all cases. Table 1 shows characteristics of patients. Serum PSA levels (Hybritech, San Diego, Calif) were determined at each follow-up examination. Treatment-related side effects and laboratory tests were determined at each follow-up examination. Treatment was discontinued early for any participants with an expected serious adverse event or with progressive disease.

In each cycle, serum PSA levels were measured every 4 weeks during the off-phases. In particular, we considered time to reach a PSA nadir during the on-phases, time of on-phases, value of PSA nadir during the on-phases, highest PSA reached during the off-phases, and time of each cycle. IAD was considered to have failed when a patient was no longer able to cycle off-treatment (PSA did not reach a level less than 0.4 ng/mL during on-phases). These patients were eligible for further systemic or local palliative treatments as considered appropriate by the treating physician. An abnominal-pelvic magnetic resonance and a total body bone scan were performed in all cases, at 6-monthly intervals during follow-up, or upon the detection of IAD failure, to determine the clinical progression of the disease.

### MATERIAL AND METHODS

#### Patients

This was a comparative, prospective, single-center study. Inclusion into this study was based on the following criteria: histologically proven adenocarcinoma of the prostate at surgery, clinically localized prostate cancer, no preoperative hormone therapy, radical prostatectomy at our institution, and biochemical failure after surgery. Between April 2004 and September 2005, a total of 44 patients fulfilled the inclusion criteria and were included in the study. After RRP, serum PSA measurements were monitored at monthly intervals during the first year of follow-up. At follow-up, rectal examination with other radiological studies (bone scan and magnetic resonance imaging) was carried out when clinically indicated.

All 44 cases exhibited a primary postoperative decrease in serum PSA to below the detection limit after RRP (0.2 ng/mL). These 44 patients were admitted to the study once PSA levels progressed over 0.4 ng/mL. At progression, PSA determinations were repeated at 2 weekly intervals. PSA progression was defined as three or more consecutive elevated PSA levels. All 44 cases showed a PSA progression no later than 12 months from RRP. For the study protocol, all 44 patients were submitted to total body bone scan, abdominal-pelvic magnetic resonance upon the detection of PSA progression. These examinations were negative in all cases. Table 1 shows characteristics of patients. Serum PSA levels (Hybritech, San Diego, Calif) were evaluated in all cases.

#### Treatment

We obtained signed informed consent in all cases before the study. Patients were offered IAD when PSA progressed over 0.4 ng/mL after RRP. The 44 cases were randomly assigned to receive two different treatment strategies: group A received IAD therapy using bicalutamide 150 mg once a day in the on-phases and no therapy in the off-phases. Group B received IAD therapy using bicalutamide 150 mg once a day in the on-phases and etoricoxib 60 mg once a day in the off-phases. In both groups the initial treatment period (cycle 1, on-phase) lasted 12 weeks in all cases. After this period an acceptable nadir was considered to be a serum PSA level of less than 0.4 ng/mL and stable or decreasing. Bicalutamide therapy was then withheld until serum PSA increased to a value of 1.0 ng/mL or greater (off-treatment phase). The subsequent on-treatment phases lasted for the time needed to again reach the PSA level less than 0.4 ng/mL with a stable or decreasing value. The length of one treatment cycle was defined as the number of weeks under on-phase followed by the number of weeks under off-phase.

### Statistical Analysis

The study objectives called for a design that would detect a statistically significant difference between measures of 25% at \( P < 0.05 \) with a power of 90% (type II or beta error of 0.1).
Using standard power analysis methods, we estimated a sample size of 22 subjects in each group of therapy.

Mean changes adjusted for baseline are presented and were tested using the Wilcoxon sign-rank test. Pairwise treatment comparisons were made. All statistical tests were two-tailed with a 5% level of significance for treatment effects.

RESULTS

A total of 44 patients with PSA progression from an undetectable PSA after RRP were evaluated and randomized in the two groups of treatment. All patients responded to their first 12 weeks of treatment with bicalutamide and serum PSA dropped to a median level of 0.20 ng/mL in group A and 0.15 ng/mL in group B (P = 0.4117). At present, 7 of 44 (15.9%) patients have failed to respond to reinstitution (on-phase) of treatment. All these cases had subsequently been withdrawn from IAD and are currently treated with continuous administration of luteinizing hormone releasing hormone analogue without evidence of clinical progression. In particular, in group A 5 of 22 (22.7%) cases (all pT3 and Gleason score 7 (4+3) or greater at RRP) failed to respond at cycle 2 (3 cases at median time 20 weeks) and cycle 3 (2 cases at median time 36 weeks); in group B, 2 of 22 (9.1%) cases (all pT3 and Gleason score 7 (4+3) or greater at RRP) failed at cycle 3 (median time 47 weeks).

No other patient in both groups demonstrated disease progression and all concluded three cycles of IAD therapy. This report concerns the results only of these first three cycles.

In group A mean follow-up from the start of IAD was 49.27 ± 13.53 weeks (median, 56 weeks; range, 20 to 60 weeks), whereas in group B it was 65.72 ± 7.23 weeks (median, 68 weeks, range 46 to 74 weeks).

Table 2 presents cycling characteristics of the patients in the two groups randomized during the 3 cycles of IAD. In particular, comparing the two groups of treatment, in all three cycles of IAD, the time of the cycles and the time of the off-phases were significantly (P < 0.0001) longer in group B than in group A.

Moreover, the highest PSA value reached during the off-phases in each cycle was significantly lower in group B than in group A (Table 2). On the contrary, no significant differences between the groups were found regarding the on-phases (time and PSA nadir) of each cycle (Table 2).
The off-therapy median time for the three treatment cycles was stable at 8 weeks in group A, whereas it increased from 10 weeks in cycle 1 (45.4% of the complete cycle) to 12 weeks in cycle 2 and 3 (54.5% of the complete cycle) in group B.

For all 37 patients (17 in group A and 20 in group B) responding to the three cycles of IAD, during follow-up all bone scan and magnetic resonance results were normal (with no evidence of metastases or local recurrence).

**Treatment Side Effects**

All patients tolerated bicalutamide therapy well during each cycle of IAD and there were no serious adverse events. As expected, all patients experienced side effects including decreased libido, erectile dysfunction, and fatigue. A total of 28 cases experienced gynecomastia but all were without significant breast pain. We found no differences between group A and group B cases. In no patient was a spontaneous erectile function restored during IAD. In group B etoricoxib treatment during the off-phases was generally well tolerated and no likely related serious side effects have been described. No significant modifications in hematology or renal and liver function tests were detected on assessment of the laboratory data. Withdrawal from treatment owing to side effects was not necessary in any of the 44 patients.

**DISCUSSION**

To our knowledge, this study represents the first experience in the literature using a COX-2 inhibitor during the off-phases of IAD therapy for prostate adenocarcinoma. Our hypothesis was to use a COX-2 inhibitor to improve the whole response to IAD and, in particular, to prolong the time of the off-phases. The intermittent administration of IAD therapy is not modified and its rationale is respected. Our aims in the administration of the COX-2 inhibitor in association with androgen deprivation therapy and in particular during the off-phases of IAD were: (1) to act on prostate microenvironment (in particular on COX-2 activity) influencing its ability to condition prostate adenocarcinoma cell growth and apoptosis; (2) to combine the direct effect on neoplastic cells of androgen deprivation therapy with the indirect (on microenvironment) effect of a COX-2 inhibitor, and (3) to sustain androgen deprivation therapy effect with the COX-2 inhibition and, in particular, to sustain the antiproliferative and pro-apoptotic effect of androgen deprivation therapy developed during the on-phase, as well as during the off-phase.

We decided to limit the use of a COX-2 inhibitor only at the off-phases of IAD because our target was specifically to prolong off-phases time during IAD and because we wanted to limit possible toxicity and side effects related to continuous administration of a COX-2 inhibitor.

We decided to analyse our hypothesis in patients with PSA progression after RRP because this rational could be particularly effective in subjects with only a biochemical progression of prostate cancer. The mechanism of action of a COX-2 inhibitor on microenvironment could be more effective as a preventive of future clinical progression than as curative of clinical evidence of recurrence or progression. Pound et al. reported a 34% rate of metastatic progression within 5 years in patients with PSA progression after RRP in the absence of adjuvant therapy. No consensus has been reached regarding the optimal indications for post-RRP hormonal therapy. To reduce the morbidity of hormonal therapy and to delay the hormone resistance of prostate cancer, the use of IAD in this type of population has been proposed by other authors. We also showed that IAD therapy can significantly reduce the increase in serum chromogranin A levels and therefore in neuroendocrine activity induced by androgen deprivation therapies.

Two ongoing, cooperative-group, phase III trials are evaluating the survival impact of IAD both in patients with metastatic disease and in those with PSA failure after primary therapy.

In the present study we used the same treatment protocol of IAD used in the previous experience. However, we decided to use an antiandrogen monotherapy during the on-phases (which is not approved for this use), as also described by Peyromaure et al. in a similar experience on cases with PSA progression after RRP. To date, it has not been determined which initial androgen deprivation therapy should be preferred during IAD. Peyromaure et al. and our present data indicate that in a population with only biochemical progression, IAD can be safely initiated with an antiandrogen alone. In particular, Peyromaure et al. showed satisfactory long-term results with a median interval between initiation of antiandrogen IAD therapy and cancer-related death of 86 months.

The COX-2 promotion of prostate cancer cell growth and modification of phenotype has been linked to its ability to promote angiogenesis, inhibit apoptosis, and modulate the microenvironment around cells. Smith et al. recently assessed the biologic activity of a COX-2 inhibitor (celecoxib) in men with recurrent prostate cancer after RRP or radiotherapy, using change in PSA doubling time (PSADT) as the primary outcome variable. Compared with placebo, celecoxib significantly decreased mean PSA-velocity and tended to increase the proportion of men who doubled their PSADT.

Our report is a comparative randomized study in which the effect of the combination of a COX-2 inhibitor to IAD was analysed in respect to IAD alone. We show that the use of a COX-2 inhibitor, also if limited to the off-phases of IAD, might: (1) significantly ($P < 0.0001$) and progressively increase the time of off-treatment phases; (2) significantly ($P < 0.0001$) reduce the highest level of PSA reached during off-phases (PSA would probably rise more slowly during off-phases); and (3) significantly ($P < 0.0001$) and progressively increase the percentage of time of the off-phases in three cycles of IAD.
compared with the use of IAD alone. Moreover, the percentage of cases that discontinued IAD because they failed to respond to reinstitution of treatment (on-phases) was lower (9.1%) in the group of IAD + COX-2 inhibitor than in the group of IAD alone (22.7%).

Some limits related to the study must be underlined. We did not determine pretreatment PSA doubling time and multivariate analyses because the comparison of different factors able to influence the response to therapy during IAD was not realizable. The current follow-up does not consent to have results in terms of survival or in terms of clinical progression. However, our positive data could justify the interest on this kind of approach and the development of larger clinical trials.

We also note that tolerability of both treatment regimens was good, none of our cases discontinued treatment, and no serious adverse events were reported. We did not perform a specific evaluation of quality of life during treatments in our population. COX-2 inhibitor long-term safety (in particular for rofecoxib) has been questioned. In our analysis the COX-2 inhibitor was used intermittently and for relatively long periods: Intermittent administration may contribute to increase safety and tolerability. Longer periods of treatment with the combination of bicalutamide and a COX-2 inhibitor may be associated with an increase in cardiovascular toxicity. As a COX-2 inhibitor we used etoricoxib, which showed higher COX-2 selectivity than others drugs (rofecoxib and celecoxib) and long-term (138 weeks) tolerability. For now this study has been discontinued pending a more complete and general revision of the safety of COX-2 inhibitors, before these drugs are used to treat prostate cancer over longer periods.

References