FinnBladder-8 – A randomized, placebo-controlled trial comparing celecoxib plus BCG to standard BCG therapy in patients with high-risk non-muscle invasive bladder cancer - A pilot study.

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Abstract

Objective: To study whether the COX-2-inhibitor, celecoxib, in combination with Bacillus Calmette-Guérin (BCG) therapy further improves the efficacy and tolerability of BCG therapy in the treatment of high-risk non-muscle invasive bladder cancer (NMIBC).

Material and methods: This study is a prospective, randomized, double-blind, multicenter, and placebo-controlled phase II pilot study with 40 high-risk BC patients from Finland between 26 May 2008 and 4 October 2012. Patients were randomized to have celecoxib or placebo for two years, and they were also given 6 weekly BCG instillations followed by 3 weekly instillations at months 3, 6, 12, 18, and 24. The primary objectives were to evaluate time to recurrence and side-effects. Secondary objectives were time to progression, time to instillation treatment failure, time to BC death or cystectomy, and overall survival.

The principal statistical methods were the proportional subdistribution hazards model and the Cox proportional hazards model.

Results: Only 40 patients were randomized, having a median follow-up of 135 months (range 7-161). Approximately half of the patients in both groups completed BCG therapy. No significant effect of celecoxib was found on recurrence or secondary objectives. However, a few significant differences favoring the celecoxib-group were observed in the QoL symptom scores, some of which were significantly associated with patient outcomes.

Conclusions: While celecoxib had no positive impact on the efficacy of BCG, it showed some tendency to improve tolerability to BCG treatment. Despite the low number of patients, some symptom scores significantly predicted patient outcomes.

Keywords: Bladder cancer, Cyclo-oxygenase 2 inhibitor, BCG treatment, Quality of life, Cytology

Introduction

Bladder cancer (BC) is the tenth most common malignancy in the world. The incidence is rising worldwide, especially in developed countries.[1] The majority, more than 70% of malignant bladder tumours, are diagnosed in the superficial stages, i.e., non-muscle invasive bladder cancers (NMIBC).[2] Typically, these tumours are characterized by an elevated risk of recurrence compared to a rather low risk of progression. The use of Bacillus Calmette-Guérin (BCG) and intravesical chemotherapy are well-known management options in trying to reduce the recurrence and progression of NMIBC. As many as 70% of patients experience local or even systemic side-effects from BCG therapy.[3]

Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor with a reported chemopreventive activity against different kind of cancers, including BC. Celecoxib has a potential to inhibit the proliferation, migration, invasion, and transition of BC cells, but the mechanism is not fully understood.[4] Currently, randomized studies do not support a clinical benefit for the use of anti-inflammatory drugs (e.g. celecoxib) in preventing recurrence of NMIBC. [3,5] However, more investigation is needed especially in high-grade BC tumours, since the immune response to cancer stimuli is probably more pronounced in advanced stages, with increased COX-2 expression associated with invasiveness and poor prognosis.[6]

In this study, we aimed to explore whether the COX-2 inhibitor, celecoxib, in combination with BCG therapy is more effective in reducing the risk of recurrence or

progression than BCG therapy alone for the treatment of high-risk NMIBC. We also wanted to clarify whether the COX-2 inhibitor improves tolerability of BCG therapy.

Material and methods

FinnBladder-8 study is a prospective, randomized, double-blind, multicenter, and placebo-controlled phase II pilot study with 40 high-risk BC patients. Inclusion criteria were carcinoma in situ (CIS) with a preceding or concurrent papillary Ta tumor (grade 1 - 3), Ta tumors of grade 3 /high grade or T1 tumors of grade 2 - 3 / high grade with or without CIS. The main exclusion criteria were decreased kidney function and increased risk of cardiovascular adverse events.

All patients were treated with 6 weekly instillations of RIVM BCG (2×10^8 - 3×10^9 CFU in 50 ml saline, Medac Gmbh) followed by 3 weekly instillations at months 3, 6, 12, 18, and 24. An oral therapy with one tablet of placebo or celecoxib 400 mg twice daily started on the first day of the BCG instillation and continued until two weeks after the last BCG instillations given at month 12. Oral therapy continued along with the BCG therapy and was given 4 weeks at months 18 and 24, starting concurrently with the first of three BCG instillations scheduled for these two months. After obtaining the informed consent, the FinnBladder office conducted the randomization. The allocation concealment and blinding were based on drug codes managed by the HUCH pharmacy that supplied the drugs to all participating hospitals.

Control visits were scheduled for every three months during the first two years, every six months for up to five years, and thereafter at least yearly. The control visits included cytology and cystoscopy. In addition, to ensure the state of no evidence of disease at 3 months, at least three select biopsies and biopsies of suspicious urothelium were taken. Side-effects and quality of life (QoL) were recorded by a questionnaire before BCG therapy started and at the end of altogether six instillation periods mentioned above.

The primary objectives in the original protocol were to evaluate time to recurrence and side-effects. Secondary objectives were time to progression, time to instillation treatment failure, disease-specific, and overall survival. In the final analysis, disease-specific survival was replaced with time to BC death or cystectomy. Recurrence was defined as occurrence of biopsy confirmed Ta tumour or CIS, or positive cytology. Progression was defined as occurrence of biopsy confirmed T1 tumour or more advanced disease. If progression was the first event without preceding occurrence of CIS, it also was included as an event in the analysis of time to recurrence. Failure of instillation therapy was defined as progression or change of therapy due to recurrence or side-effects during the first year, while after the first year the failure was defined as recurrence, progression, or change of therapy.

RStudio 2023.09.1, build 494, was used for statistical analyses. The Fisher's exact test was used in cross tabulations. Overall survival was analysed with Cox proportional hazards model, while the cumulative incidence analysis and the proportional

subdistribution hazards model, that is, the competing risks regression (CRR) were used for other endpoints, with deaths from other causes than BC regarded as competing events. In some extreme cases of CRR with no endpoint events observed in either of the two groups, the number of patients with no endpoint event and with the event in both groups were compared using Fisher's exact test. Due to the small number of patients and the substantial amount of QoL data missing already in their initial scores before treatment and increasingly during follow-up, a simplified assessment of QoL data was made. As combining the data of bother scores with the basic scores did not affect the outcome in our preliminary analyses, only the basic scores were used in the final analysis. As for the most important analysis, the initial pre-treatment scores of each basic score category were compared separately in both treatment groups pairwise with the corresponding scores at six follow-up time points using the non-parametric Wilcoxon rank sum test. In addition, the distribution of scores in each category between the two treatment groups at all time points, including the pre-treatment time point, was compared using the Wilcoxon's signed rank test. Moreover, to explore possible trends, as the number of patients was small, all scores of same categories from six time points were pooled in both treatment groups and the distributions were compared with the pre-treatment scores. The Wilcoxon's signed rank test was used in all comparisons involving pooled score distributions.

As for possible predictors in the proportional hazards and subdistribution hazards models, the basic pre-treatment QoL scores of each category were included in the analyses in addition to the more conventional factors, such as T category, grade, and cytology. Albeit being categorical variables, the pre-treatment scores were initially

treated as continuous variables to find possible significant predictors. In the final analysis, dichotomous values of score categories were created. The analyses were performed both for patients with complete data only and for all patients, with missing data substituted with the mean of the variable. The cut-off level of statistical significance was set at $p < 0.05$ in all tests.

Ethical committee approved the protocol that was conducted in accordance with the Declaration of Helsinki. The Pfizer Foundation, New York (Investigator Request for Independent Researcher Grant) sponsored the study. All the funding was transferred and monitored by the Clinical Research Institute HUCS Ltd.

Results

Between 26 May 2008 and 4 October 2012, 40 patients were recruited from three centers in Finland. Of these patients, 19 were randomized to the celecoxib-group and 21 to the placebo-group. The overall median follow-up time was 135 mo (range 7-161 mo). The demographics and clinical characteristics of the study patients are shown in Table 1.

Approximately half of the patients in both groups completed BCG therapy; 52.6% (10/19) in the celecoxib-group and 52.4% (11/21) in the placebo-group. None of the

patients in the celecoxib-group changed or discontinued BCG therapy due to adverse symptoms, while in the placebo-group four of ten patients had adverse symptoms leading to a BCG instillation protocol deviation.

Main outcomes of treatment

No significant differences were found between the celecoxib-group and the placebo-group regarding time to recurrence, time to instillation treatment failure, time to BC death or cystectomy, or overall survival (Fig 1A-D). Concerning Fig.1C, only two patients in the celecoxib-group and one in the placebo-group died of BC, with the rest of events being due to cystectomies. Five cystectomies were performed in both groups. In the celecoxib-group, all the cystectomies were performed due to BC recurrence or progression, while in the placebo-group two cystectomies were done because of adverse urinary symptoms.

Only one patient, who had been cystectomized, died of BC. Overall, seven patients died in the celecoxib-group and five in the placebo-group. Four patients died of lung cancer, three of BC, two of colon cancer, in addition to single cases of pneumonia, deterioration of general condition, and non-specified sudden attack.

Quality of life

Of the 19 vs. 20 patients in the celecoxib- vs. placebo-group, 79% vs. 75% completed their QoL questionnaire before treatment, with the response rates decreasing during the treatment to the percentages of 79 vs. 75, 68 vs.65, 68 vs.65, 68 vs. 50, 53 vs. 40, and 53 vs. 60 at 1.5, 3, 6, 12, 18, and 24 mo, respectively. There were no significant

differences in the distributions of the individual pre-treatment score categories between the treatment groups. However, the p value was 0.08 between the scores of dysuria, with scores higher in the placebo-group.

Comparing individual pre-treatment scores to those at each time point in the celecoxib-group, the frequency of urination in the daytime was significantly lower at 6 mo, urinary problems were significantly less severe at 12 and 18 mo, and mental health was significantly improved at 12 mo. In the placebo-group, there were significantly more chills at six and 24 mo, and mental health was significantly improved at 12 mo.

Comparing distributions of individual score categories between the treatment groups at each timepoint during the treatment, all significant differences favored the celecoxib-group. Compared with the celecoxib-group, there were in the placebo-group significantly more joint and/or muscle pain at 1.5 and 12 mo, more chills at 3 and 12 mo, more hematuria at 6 mo, and more bladder pain at 18 mo.

Comparing the distribution of pretreatment scores with those of pooled scores during the treatment separately in the two groups, the only significant difference was in the scores of chills, with scores higher during treatment than before treatment in the placebo-group ($p=0.02$).

There were no significant changes between the pre-treatment and 24-month scores regarding the overall urinary problems or mental well-being in either group.

Predictors of response

Table 2A shows the results of the univariable analysis, including the variables that were significant predictors of one or several endpoints. Separate analyses were performed for

a smaller number of patients with complete data and for all patients, with missing data substituted with the mean of a variable. There were some extreme results in patients with complete data, as those with no urgency had no events of recurrence and thus neither instillation treatment failure nor BC death or cystectomy. Similarly, those without dysuria had no events of BC death or cystectomy.

Based on the results of the univariable analysis, the multivariable analysis was performed on the two endpoints, instillation treatment failure, and BC death or cystectomy, substituting the missing data with the mean of the variable. Of the four variables above, urgency and nocturia were significantly associated in that all but one patient with nocturia also had urgency (p=0.005, Fisher's exact test), which is why nocturia was excluded from the analysis. With including cytology, urgency and dysuria simultaneously in the model, they were all significantly associated with the two endpoints, apart from dysuria with instillation treatment failure (p=0.06).

Discussion

In our randomized and placebo-controlled pilot study with the median follow-up of 135 months, we compared BCG therapy with or without celecoxib medication in high-risk NMIBC patients. With respect to our principal objectives, we found no positive impact of celecoxib on recurrence. However, we observed a few significant differences favoring

the celecoxib-group in the QoL symptom scores, some of which were additionally significantly associated with patient outcomes.

The weakness of our study is the lack of power caused by premature termination of the study due to economic reasons.

There are two other studies combining BCG therapy with celecoxib medication, having median follow-up times of 12 and 44 mo in contrast the 135 mo of our study .[7,5] The earlier study consisted of 146 patients having recurrence-free rates of 74% for celecoxib and 60% for placebo at 2 years. [7] In the Boxit trial,[5] among 346 high-risk BC patients the corresponding rates were 75% and 68%, respectively, at 3 years.

The earlier study performed initially like ours, whereas the Boxit trial showed better recurrence-free rates at 3 years.

In both above studies, there was a trend for better outcome in celecoxib-groups, and in the subgroup analysis of the Boxit study, a significance level was reached for T1 tumours. This contrasts with our study, in which more recurrences appeared in the celecoxib-group in the early phase, leading to permanent non-significant difference of about 20% in the risk of recurrence in favor of the placebo-group. However, compared with the two studies, the patients in our study had a higher proportion of T1 tumors and CIS, indicating a particularly high-risk for progression.

In our study, only one patient with progression received oncological treatment afterwards. The reported progression rate of 10% in the Boxit trial is higher than in our study. Ten cystectomies in our study were equally distributed between the two treatment

groups. The reasons for cystectomies were recurrent disease in eight patients and severe urinary symptoms in two, both belonging to the placebo group. It is noteworthy that no cystectomies were done because of disease progression. The prompt cystectomies due to recurrence, without actual progression, may explain our low progression rate.

The risk of progression and BC mortality varies from study to study. We had no BC deaths during the 2-year therapy time. The Boxit trial reported a relatively low BC mortality rate of 4% (19/472 patients) after 44 mo, while our rate after a median of 135 mo was less than 10% (3/40). However, BC is a potentially life-threatening disease. A review study of high-grade BC patients found a wide variation in reported progression rates (8-54%) and in BC mortality (6-46%), with follow-ups ranging from 48 to 123 mo.[8]

Overexpression of COX-2 is observed in many cancer types, including BC.[9] Among BC patients, COX-2 is expressed in 70-85% of patients with CIS and in at least 62% of those with T1 disease.[10,11] Although epidemiological and clinical prospective data have shown that COX-2 inhibitors possess a potential chemopreventive effect on various cancers including colon, breast, and prostate,[12] we were unable to find such effects in our clinical pilot study.

The detection of unexpected adverse effects caused by coxib medication has led to the premature termination of two large prospective trials because of the increased risk of thromboembolic events.[13,14] The Kaplan-Meier analysis of these studies showed that the

separation of cardiovascular events between the groups started no earlier than after 12-18 months of treatment, which may suggest that the risk of adverse events does not increase if the use of celecoxib is less than 12-18 months. Only one patient in our study had a thromboembolic event, with the patient belonging to the placebo group.

BCG is a well-proven treatment in high-risk NMIBC, and its side-effect profile is well-known. BCG therapy may cause side-effects such as urgency, hematuria, and infections.[3,15] In the QoL questionnaire, the most common symptoms were nocturia, urgency, dysuria, and fatigue. Intensity and prevalence of each measured symptom varied only a little during the follow-up, and only some statistically significant differences favoring the celecoxib-group were observed. A Nordic study[16] showed that patients with T1 high-grade BC have disease-specific symptoms already before the start of BCG instillations and the same was noted in our study. However, side-effects during BCG treatment can be severe enough to discontinue instillations. It is important to evaluate whether the symptoms are related to BCG treatment or to BC itself.[16] Even though the differences in the QoL scores between the groups were small, it is noteworthy that five patients of ten discontinued the treatment because of side-effects, with no such discontinuations in the celecoxib-group. We observed neither poorer compliance in the celecoxib-group unlike reported earlier.[5]

Interestingly, our results showed that the absence of some irritative bladder symptoms was significantly associated with better patient outcomes. Patients with no urgency had no BC recurrence and needed no additional treatment during the follow up. Similarly, among patients with complete data, only one patient with no dysuria was considered an

instillation treatment failure, while all patients who underwent cystectomy or died of urothelial carcinoma had initially had dysuria. Based on a meta-analysis, the specificity of cytology was 95 % and sensitivity of 37%.[17] According to another study, the sensitivity for low-grade tumors was only 16% in contrast to 84% for high-grade tumors.[18] It is thus reasonable to question whether benign cytology simply implies missed positive cytology in patients at high-risk of progression like in those of our study. However, we also found a significant association of positive pretreatment cytology with instillation treatment failure, BC death or cystectomy, and even survival. The significant associations between cytology and the above endpoints were observed in the multivariable analysis and only when missing data were substituted with the mean. The association of cytology with survival obviously reflects the fact that, within the limits of very low numbers, 50% of patients (8/16) with malignant cytology had died (mainly in various carcinomas) by the end of the study in contrast to less than 20% of those (3/16) with benign cytology. As for further follow-up after cystectomy, cytology does not appear to be a potent screening tool for finding early upper urinary tract recurrences.[19]

The outcome of our pilot study does not support the use of celecoxib as an adjunct to BCG instillation therapy. However, some of our findings weakly suggest that NSAID-type oral therapy may improve the tolerance to BCG therapy, even to the extent that some may avoid cystectomy as a result. Additionally, it seems worth exploring whether the significant associations found in our study between the absence of some urinary symptoms and the patient outcomes exist in a patient cohort substantially larger than ours.

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Table 1. Characteristics of the study patients.

	Study group N= 40	Celecoxib N=19	Placebo N=21	p-value
Age, mean (range)	65.2 (40.6-83.3)	62.9 (40.6-79.4)	67.3 (45.9-83.3)	0.122
Sex				0.124
male (%)	35 (87.5)	15 (78.9)	20 (95.2)	
female (%)	5 (12.5)	4 (21.1)	1 (4.8)	
Bladder vol (ml), mean (range)	402 (200-900)	399 (204-900)	406 (200-695)	0.409
Epirubicin 50/100mg				**0.039**
Yes (%)	19 (47.5)	6 (31.6)	13 (61.9)	
No (%)	20 (50.0)	13 (68.4)	7 (33.3)	
NA (%)*	1 (2.5)		1 (4.8)	
PAPA				0.446
1 - 2 (%)	7 (17.5)	5 (26.3)	2 (9.5)	
3 (%)	9 (22.5)	4 (21.1)	5 (23.8)	
4 - 5 (%)	16 (40.0)	8 (42.1)	8 (38.1)	
NA (%)*	8 (20.0)	2 (10.5)	6 (71.4)	
pT stage				0.862
CIS (%)	8 (20.0)	3 (15.8)	5 (23.8)	
CIS+Ta (%)	6 (15.0)	4 (21.1)	2 (9.5)	
CIS+T1 (%)	5 (12.5)	2 (10.5)	3 (14.3)	
Ta (%)	3 (7.5)	1 (5.3)	2 (9.5)	
T1 (%)	18 (45.0)	9 (47.4)	9 (42.9)	
Gradus				0.388
Gradus 2 (%)	8 (20.0)	5 (26.3)	3 (14.3)	
Gradus 3 (%) inc. in situ	31 (77.5)	14 (73.7)	17 (81.0)	
NA (%)*	1 (2.5)		1 (4.8)	
Diameter of tumor (mm), mean (range)	29.4 (5.0-70.0)	24.5 (5.0-53.0)	34.3 (10.0.-70.0)	0.342
Number of tumors, mean (range)	2 (0-35)	3 (0-35)	1 (0-2)	0.076
**	1 (0-4)	1 (0-4)	1 (0-2)	0.124
Number of BCG instillations, mean (range)	18 (3-27)	17 (6-21)	18 (3-27)	0.366

*information not available

** one patient (number of tumors 35) excluded from the analysis

Table 2.

	Endpoint											
	Recurrence			Instillation treatment failure			BCa death or cystectomy			Overall survival		
Variable	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
cytology (benign vs. malignant)*	0.6	0.26-1.8	0.5	2.9	0.92-9.4	0.07	3.5	0.95-13.1	0.06	3.5	0.92-13.1	0.07
cytology (benign or missing vs. malignant)	0.9	0.37-2.3	0.9	3.7	1.3-10.7	0.02	4.0	1.3-12.9	0.02	3.9	1.2-13.2	0.03
urgency (never or missing vs. sometimes to always)	3.2	1.1-9.1	0.03	2.9	0.9-9.1	0.08	2.1	0.67-7.0	0.2			NS
nocturia (none or once vs. more frequently)*	2.7	0.87-8.1	0.09	5.1	1.2-22	0.03	8.4	1.1-66.2	0.05			NS
nocturia (none or once or missing vs. more frequently	2.1	0.85-5.3	0.1	3.2	1.1-9.5	0.03	3.4	1.0-11.1	0.05			NS
dysuria (never vs. sometimes to always) *	2.4	0.86-6.8	0.09	5.2	1.6-16.7	0.005	7.87	2.5-24.6	<0.001			NS
dysuria (never or missing vs. sometimes to always)	1.8	0.71-4.74	0.2	3.2	1.0-10.3	0.05	3.8	1.0-14.2	0.05			NS

* Missing values

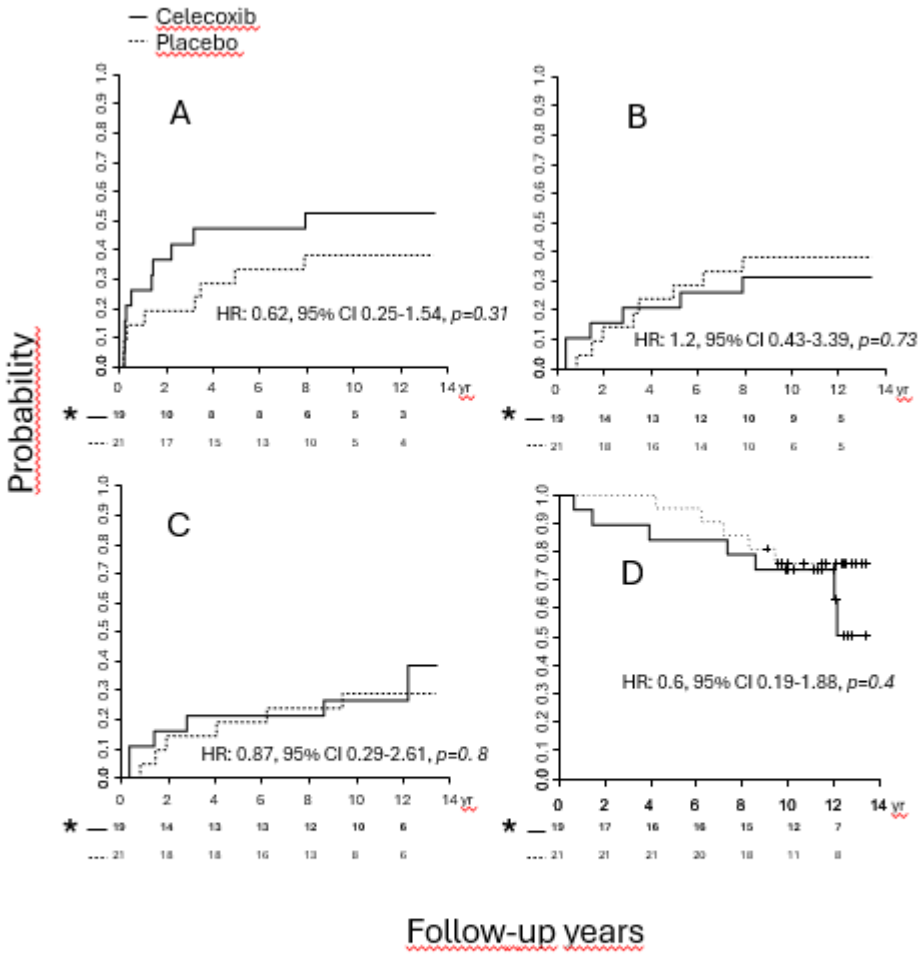

Figure 1. Cumulative incidence (A-C) or Kaplan- Meir (D) plots showing the main outcomes of treatment. A) time to recurrence, B) time to instillation treatment failure, C) time to BC death or cystectomy, D) overall survival.

* Patients at risk