ORIGINAL PAPER

Long-term results of a single-center prospective randomized trial assessing efficacy of a shortened course of adjuvant chemotherapy after radical cystectomy in patients with locally advanced bladder cancer

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Introduction This study assesses the efficacy and tolerability of two cycles of adjuvant chemotherapy (AC) with gemcitabine and cisplatin after radical cystectomy in patients with a high risk of progression of muscle-invasive urothelial bladder cancer as compared to chemotherapy at relapse, in a prospective randomized study.

Material and methods From 2008 to 2013, all patients after radical cystectomy at our institution for primary or recurrent urothelial bladder cancer with stage pT3-4 and/or pN+ on histopathology and without contraindications to combination cisplatin-based chemotherapy, were randomized either to two cycles of gemcitabine and cisplatin chemotherapy or to follow-up and chemotherapy at the time of relapse. The study endpoints were overall, cancer-specific, and disease-free survival.

Results The study included 100 patients, of whom 53 received AC and the other 47 were assigned to the control arm. Out of 53 allocated to AC arm, 16 patients did not start chemotherapy or received only one cycle of AC. The median follow-up for patients in the AC and control arms was 88 and 86 months, respectively. In the AC arm the hazard ratio for death from any cause, death from bladder cancer, and disease relapse were 0.70 (95% CI 0.45–1.11; p = 0.13), 0.84 (95% CI 0.50–1.41; p = 0.51), and 0.77 (95% CI 0.46–1.28; p = 0.31), respectively.

Conclusions Two cycles of AC with gemcitabine and cisplatin in patients with high-risk urothelial bladder cancer after radical cystectomy does not improve overall, cancer-specific, and disease-free survival. Only 53% of patients randomized to AC received the entire planned treatment.

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INTRODUCTION

Bladder cancer ranks twelfth in worldwide cancer incidence with over 549,000 new cases and about 200,000 deaths annually [1]. Muscle-invasive bladder cancer is a highly lethal disease commonly requiring immediate radical cystectomy (RC) with pelvic lymph node dissection and urine diversion [2]. Despite aggressive treatment, survival after RC in patients with pathologically locally advanced bladder cancer does not exceed 50% [3, 4].

Neoadjuvant cisplatin-based combination chemotherapy is a standard strategy to improve treatment outcomes in patients with muscle-invasive bladder cancer undergoing RC with level 1 evidence of survival benefit [5]. However, adjuvant chemotherapy (AC) can be an alternative approach, the advantage of which is a more accurate selection of patients

for this treatment [6]. One of the major drawbacks of AC is a need to provide rather toxic treatment in a patient population with a high frequency of complications following morbid surgery, which precludes a full course of AC in 26–48% of patients [7, 8, 9]. A shortened course of treatment (e.g. two cycles of chemotherapy instead of 3–4), might improve treatment tolerance and acceptance for both patients and physicians. This study aimed to assess the efficacy and tolerability of AC with two cycles of gemcitabine and cisplatin in patients with muscle-invasive urothelial bladder cancer at high risk of progression after RC.

MATERIAL AND METHODS

Between September 2008 and October 2013, all patients within 8 weeks of RC for primary or recurrent urothelial bladder cancer were considered for inclusion in a prospective randomized study. In practice, we selected our patients at discharge from our institution after RC (usually 1 to 3 weeks after surgery). Inclusion criteria were histologically proven tumor invasion into perivesical fat and/or prostate stroma, or metastatic spread to pelvic lymph nodes; age at least 18 years; absence of contraindications to cisplatin-based combination chemotherapy that included WHO performance status <2, adequate bone marrow reserve, estimated glomerular filtration rate ≥70 ml/min, adequate hepatic function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase <2.5 times upper limit of normal), and absence of clinically significant heart diseases, or peripheral neuropathy grade 2 or more. All patients were required to sign informed consent to participate in the protocol. Patients with invasive malignancies except low-risk prostate cancer, and with a history of systemic cisplatin-based chemotherapy or pelvic radiotherapy were excluded from the study.

The patients meeting the inclusion and exclusion criteria were randomized into two groups. In the experimental arm, patients received two cycles of AC. The chemotherapy regimen included administration

Table 1. *Patient characteristics*

Characteristic	Adjuvant chemotherapy arm	Control arm	Total
Age, median (IQR)	61 (55.67)	62 (53.67)	62 (54.67)
Gender, n (%)			
female	4 (8)	6 (13)	10 (10)
male	49 (92)	41 (87)	90 (90)
Recurrent status, n (%)			
primary	11 (21)	15 (32)	26 (26)
recurrent	42 (79)	32 (68)	74 (74)
WHO performance status, n (%)			
0	38 (72)	36 (77)	74 (74)
1	15 (28)	11 (23)	26 (26)
Morphological variant, n (%)			
pure urothelial	39 (74)	30 (64)	69 (69)
with squamous differentiation	12 (23)	13 (28)	25 (25)
with glandular differentiation	2 (4)	4 (9)	6 (6)
Tumor grade (WHO, 1973), n (%)			
G 1–2	19 (36)	10 (21)	29 (29)
G 3–4	34 (64)	37 (79)	71 (71)
pTNM, n (%):			
pT3aN0	5 (9)	6 (13)	11 (11)
pT3bN0	11 (21)	9 (19)	20 (20)
pT4aN0	11 (21)	11 (23)	22 (22)
pT2-4aN1	8 (15)	7 (15)	15 (15)
pT2-4aN2	18 (34)	14 (30)	32 (32)
Urine derivation, n (%)			
neobladder	42 (79)	31 (66)	73 (73)
heterotopic pouch	2 (4)	1 (2)	3 (3)
ileal conduit	6 (11)	9 (19)	15 (15)
cutaneous ureterostomy	3 (6)	6 (13)	9 (9)
Total, n (%)	53 (100)	47 (100)	100 (100)

IQR – interquartile range; WHO – World Health Organization

of cisplatin with prehydration at 75 mg/m² on day 1 or 2 of the cycle, and gemcitabine at 1000 mg/m² on days 1, 8, and 15. Cycles were repeated every 28 days. Patients in the control arm were observed, with the intention of starting chemotherapy at the time of relapse. Randomization was performed by a computer software generating random numbers with an equal allocation ratio. The procedure was done in the central randomization office via local computer network interface, which allowed concealment of the generated random sequence.

Follow-up for patients after AC and those in the control arm included physical examination, ultrasonography or computed tomography of the abdomen and pelvis, and chest X-ray every 3 months in the first year, then every 6 months for 2–5 years, and, thereafter, every 12 months until death.

The study protocol was approved by the institutional Scientific Board according to the national legislation. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

The primary study endpoint was overall survival, defined as the time from randomization to death from any cause or the end of follow-up. Cancer-specific survival and disease-free survival were also studied. The former was defined as the time from randomization to bladder cancer death, whereas the latter was referred to as the time from randomization to local or systemic relapse or bladder cancer death. In addition, safety and tolerability of AC were assessed. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 [10]. The required number of cases in the study was estimated based on the planned therapy efficacy in reducing the relative hazard of death by 50%, and alpha and beta errors of 5% and 20%, respectively, with a minimum dropout rate.

Survival was calculated using the Kaplan-Meier method according to the intention-to-treat principle. The difference in survival between study arms was assessed with Cox proportional regression analysis by calculating hazard ratio (HR) values, their 95% confidence intervals (CI) and two-sided p-values. A p-value of <0.05 was considered to be statistically significant. The software packages STATISTICA V7.0. (StatSoft, Inc., Tulsa, OK) and IBM SPSS V21.0. (Armonk, NY) were used for the statistical analysis.

RESULTS

Over the five years, a total of 100 patients were included in the study, 53 patients were randomly allo-
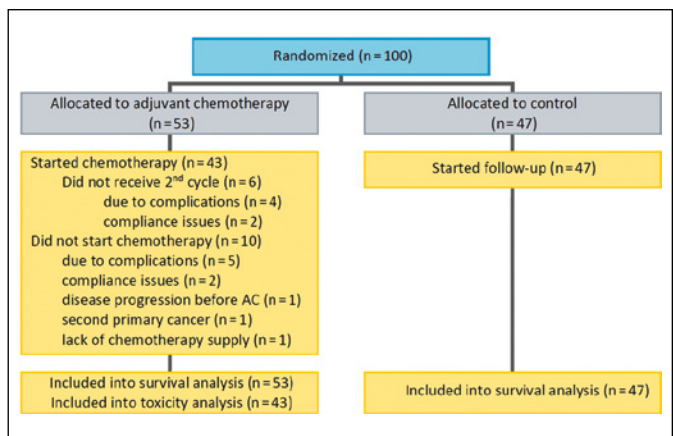

Figure 1. *CONSORT diagram.*

Table 2. *Patients status at the end of follow-up*

Patients status	Adjuvant chemotherapy arm	Control arm	Total
Alive at the end of follow-up	18 (34)	8 (17)	26 (26)
Dead of bladder cancer	30 (57)	28 (60)	58 (58)
Dead of other causes	5 (9)	11 (23)	16 (16)
Disease reccurence or death of bladder cancer	30 (57)	29 (62)	59 (59)
Total	53 (100)	47 (100)	100 (100)

cated to the AC arm and 47 to control. Patient characteristics are shown in Table 1. Of the 53 patients assigned to the AC arm, 10 (19%) patients did not start chemotherapy because of surgical complications, lack of compliance, early progression, chemotherapy agent shortage, or diagnosed lung cancer (Figure 1). Another six patients received only one cycle of chemotherapy due to treatment complications and lack of compliance. Thus, only 37/53 (70%) patients assigned to the AC arm started the second cycle of chemotherapy. Among those patients, regimen modification (chemotherapy dose reduction or interval increase) was required in another 9 (24%) due to the adverse events of chemotherapy.

Chemotherapy toxicity was assessed in 43 patients who started treatment (Table 2). The most frequent complications were hematological, with the rate of Grade III–IV complications ranging from 2% to 9%. A total of 11 (26%) patients developed Grade III–IV complications.

Median follow-up for patients in the AC and control arms was 88 (range 11–117), and 86 (range 36–108) months, respectively. During this period, out of 100 patients included in the study, 74 (74%) patients

Table 3. *Adverse events of adjuvant chemotherapy*

| Adverse event	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Leucopenia, n (%)	26 (60)	9 (21)	14 (33)	4 (9)*	–
Thrombocytopenia, n (%)	27 (63)	20 (47)	2 (5)	4 (9)	1 (2)
Anemia, n (%)	27 (63)	26 (60)	1 (2)	–	–
Nausea/vomiting, n (%)	13 (30)	9 (21)	2 (5)	2 (5)	–
Fever/infection, n (%)	13 (30)	6 (14)	6 (14)	1 (2)	–
Bilirubin/AST/ALT increase, n (%)	7 (16)	7 (16)	–	–	–
Fatigue, n (%)	7 (16)	4 (9)	3 (7)	–	–
Renal failure, n (%)	3 (7)	1 (2)	2 (5)	–	–
Myocardial infarction, n (%)	1 (2)	–	1 (2)	–	–
No of patients with any adverse events, n (%)**	40 (93)	37 (86)	21 (49)	10 (23)	1 (2)

* including one febrile neutropenia case; ** the total exceeds 100% as several adverse events could be observed in one patient; AST – aspartate aminotransferase; ALT – alanine aminotransferase

died, including 58 from bladder cancer. Patients status by treatment arm at the end of follow-up is shown in Table 3.

In the AC arm, 5-year overall survival was 35% and median survival was 23 months (95% CI 7–38 months) versus a 5-year overall survival of 27% and a median survival of 25 months (95% CI 12–39 months, Figure 2) in the control arm. The HR of death from any cause in the AC arm was 0.70 (95% CI 0.45–1.11; p = 0.13). The 5-year cancer-specific survival was 42%, and the median survival was 24 months (95% CI 0–52 months) in the treatment arm; the respective values in the control arm were 37% and 34 months (95% CI 7–62 months, Figure 3). The HR of cancer death with AC was 0.84 (95% CI 0.50-1.41; p = 0.51). The five-year disease-free survival in the AC and control arms was 43% and 36%, respectively (Figure 4). Median disease-free survival was 16 months (95% CI 5-27 months) and 16 months (95% CI 0.4–31 months), respectively. The HR of disease progression in the AC arm was 0.77 (95% CI 0.46–1.28; p = 0.31). Subgroup analysis for overall survival stratified by various patients or tumor characteristics and type of surgical procedure is shown in Figure 5.

DISCUSSION

Muscle-invasive bladder cancer is a highly aggressive disease. Not uncommonly, subclinical tumor dissemination is already present at the time of RC, which leads to subsequent clinical progression and cancer-specific mortality. The most unfavourable treatment outcomes are observed in patients with extravesical tumor spread (pT3/T4) or regional lymph nodes metastases (pN+), for which relapse rates after RC reach 38–50%, and 65-67%, respectively [3, 4].
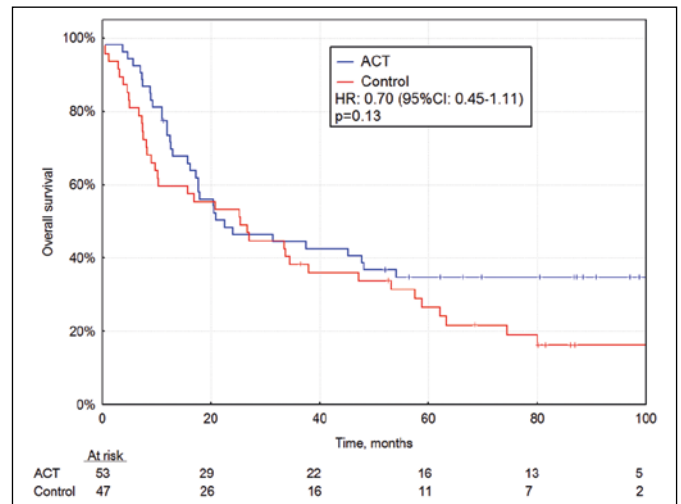
Figure 2. *Overall survival by treatment arm.*
ACT – adjuvant chemotherapy arm; HR – hazard ratio
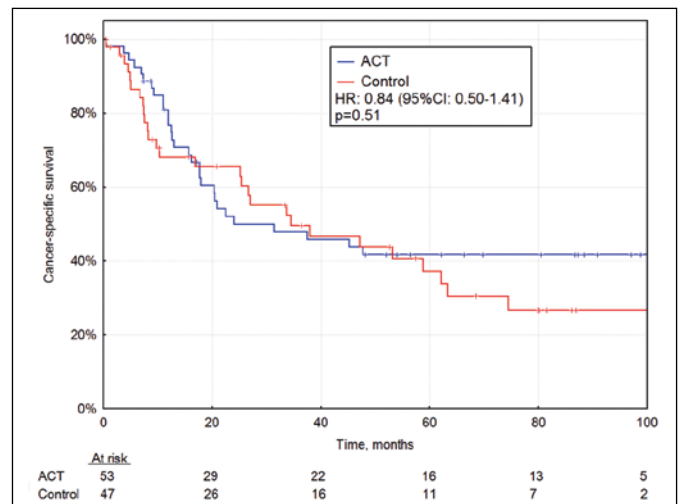
Figure 3. *Cancer-specific survival by treatment arm.*
ACT – adjuvant chemotherapy arm; HR – hazard ratio

Technological advances in surgery, such as robot-assisted operations [11, 12] and, apparently, extended lymph node dissection [13] have not significantly improved long-term outcomes, and only perioperative cisplatin-based chemotherapy has been shown to increase survival of patients with muscle-invasive bladder cancer after RC [14]. Despite more solid scientific evidence supporting the efficacy of neoadjuvant chemotherapy, many clinicians still perceive AC as a more attractive treatment strategy compared to upfront chemotherapy, as it allows for not only early local control of the tumor and related complications (haematuria, pain, etc.) through surgery, but also better targeting of patients who have the highest risk of disease progression, as clinical staging is not reliable enough and the histopathological stage remains the main prognostic factor [15, 16].

A number of prospective randomized trials had been conducted to assess the efficacy of AC after RC, and their results were summarized in several meta-analyses [17, 18]. The first meta-analysis of individual patients' data from six trials with a total of 491 patients reported a statistically significant, 25% relative reduction in the risk of death with AC as compared to the control, which was translated in the absolute survival improvement of 9% (95% CI 1% to 16%) at 3 years [17]. However, the meta-analysis concluded that despite these results, "...there is insufficient evidence on which to reliably base treatment decisions" mainly due to a small sample size available for analysis and methodological problems in the source studies.

In 2014 a new meta-analysis came out that included additional data from the three trials published after 2006 and a total of 945 patients from nine randomized controlled trials, showing statistically marginal improvement in overall survival with pooled HR 0.77 (95% CI 0.59–0.99; p = 0.049) [18].

The largest study on AC efficacy was published in 2015 and had not been included in the previous meta-analysis [19]. This study enrolled only 284 patients instead of the planned 660, and it did not show a significant improvement in overall survival with AC after RC. Also, an update on the prior meta-analysis including new data was presented in this publication, and the results suggested a benefit of adjuvant treatment in overall survival (HR 0.77; 95% CI 0.65–0.91; p = 0.002), however with significant heterogeneity between individual trials [19].

One of the main drawbacks of AC is poor chemotherapy tolerance in patients after major surgery with a large number of early and late complications [20]. In some randomized controlled trials included in the meta-analysis by Leow et al., only 52–74% of patients assigned to the AC group received the
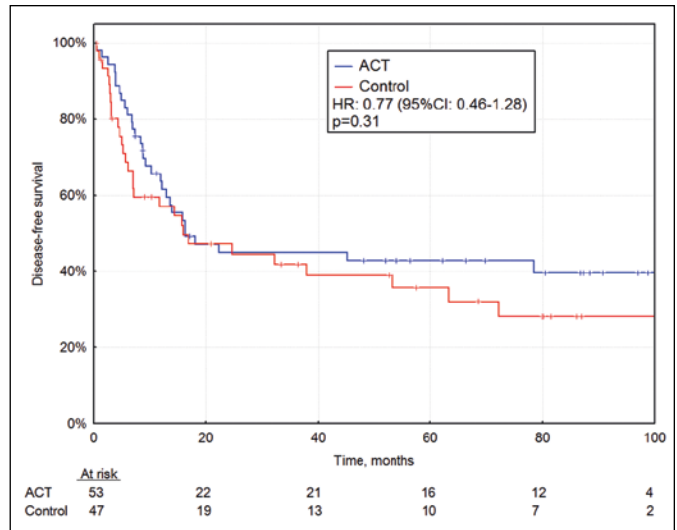

Figure 4. *Disease-free survival by treatment arm.*

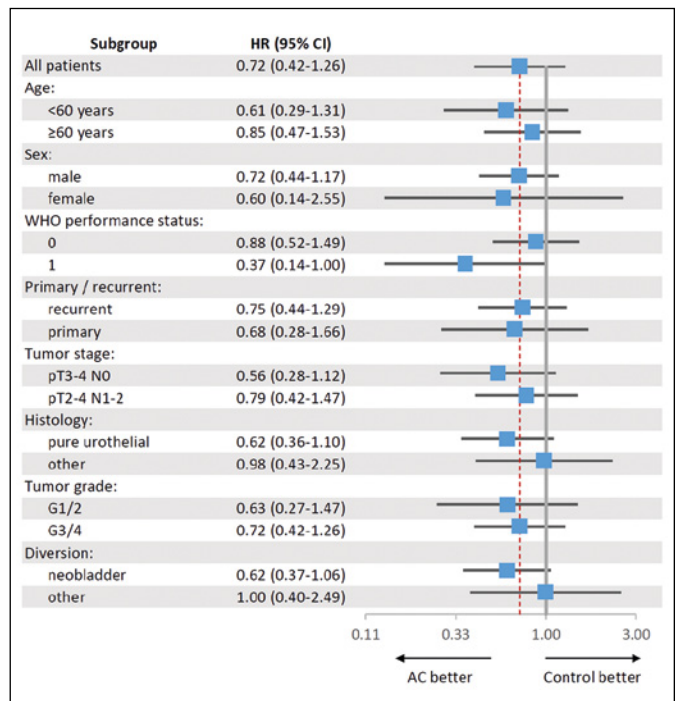*ACT – adjuvant chemotherapy arm; HR – hazard ratio*

Figure 5. *Subgroup analysis for overall survival.*

ACT – adjuvant chemotherapy arm; HR – hazard ratio

planned treatment [18]. In the landmark EORTC 30994 trial, 9% of patients in the immediate treatment group did not start chemotherapy and 20% did not receive all four cycles of AC [19]. This provided a rationale for a shortened treatment course in our study. Chemotherapy with only two cycles could potentially decrease the total burden of the treatment, alleviate the adverse effects of AC and

increase tolerance and acceptance of such therapy. Unfortunately, our study did not confirm these assumptions. Despite a shortened treatment course, only 53% of patients randomized to the AC arm received treatment according to the protocol, 19% did not start chemotherapy, and 28% received one cycle of AC or had dose modification. The most common reasons for not following the planned regimen were complications after the previous treatment and lack of compliance.

Given the low treatment intensity in the experimental arm, our study had very few chances to demonstrate the efficacy of the planned AC, and the study results are quite predictable and explainable. However, from our point of view, there are some important lessons to be taken from our study. It has been shown that the strategy of primary RC followed by AC is impractical as such treatment is most likely not to be received. The administration of neoadjuvant chemotherapy is significantly more reasonable, which is also confirmed by other authors. For instance, in the study by Millikan et al. comparing the efficacy of 2 cycles of neoadjuvant MVAC chemotherapy, followed by RC plus 3 more cycles of adjuvant MVAC, or RC with 5 cycles of AC, 97% of patients in the neoadjuvant group received at least 2 cycles of chemotherapy comparing to only 77% in the adjuvant group which received at least 2 cycles [9].

CONCLUSIONS

AC with two cycles of gemcitabine and cisplatin in patients with urothelial bladder cancer at a high risk of progression after RC does not improve overall, cancer-specific, and disease-free survival. Only 28 (53%) of the 53 patients randomized to AC received the entire planned treatment. The study was underpowered to detect the clinically meaningful benefits of AC.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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