

Combined Chemoradiation Therapy With Twice-Weekly Gemcitabine and Cisplatin for Organ Preservation in Muscle-Invasive Bladder Cancer: Long-Term Results of a Phase 1 Trial.

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Abstract: Purpose: Concomitant treatment with radiotherapy and cisplatin (CDDP) remains the gold standard for bladder preservation in case of muscle-invasive bladder cancer (MIBC). We present the long-term results of a phase I clinical trial to assess the association of gemcitabine (given twice/week) with CDDP and radiotherapy in this setting.

Methods and Materials: Patients with pT2-pT4 N0 M0 MIBC without hydronephrosis or diffuse carcinoma in situ were enrolled in this study. After maximal transurethral resection of the bladder tumor, patients received concomitantly radiotherapy (63 Gy in 1.8 fractions) and chemotherapy (20 mg CDDP /m²/day over 4 days every 21 days; and gemcitabine twice a week). The starting dose of gemcitabine was 15 mg/m² with dose escalation to 20, 25 and 30 mg/m². The primary endpoint was the determination of the maximum tolerated dose (MTD). Secondary endpoints included the assessment of toxicity and tumor control.

Results: Fourteen patients were enrolled. Dose-limiting toxicity (DLT) occurred in two patients treated with 30 mg/m² gemcitabine (grade 4 thrombocytopenia and severe impairment of the WHO performance status, respectively). Nine patients received the complete chemo-radiotherapy protocol. The recommended dose of gemcitabine was 25 mg/m². The median follow-up was 53 months, and the overall and disease-specific survival rates were 62% and 77% at 5 years, respectively. Among the patients who received the complete treatment, bladder-intact survival was 76% at 5 years and the median overall survival 69.6 months.

Conclusions: This regimen was well-tolerated. The gemcitabine MTD was 25 mg/m². Bladder preservation and disease control were promising. A multicenter phase II randomized trial is ongoing.

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Dear Editor,

Here is the second revised version of our manuscript entitled “Combined Chemoradiotherapy with Twice Weekly Gemcitabine and Cisplatin for Organ Preservation in Muscle-invasive Bladder Cancer: Long-term Results of a Phase I Trial” (ROB-D-13-01170). The manuscript has been review and corrected by the team of the Mount Sinai in New York.

We hope that all minor grammatical errors are now corrected.

Sincerely yours,

Pr David AZRIA

Combined Chemoradiotherapy with Twice Weekly Gemcitabine and Cisplatin for Organ Preservation in Muscle-invasive Bladder Cancer: Long-term Results of a Phase I Trial

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Conflict of interest: none

Running title: Conservative bladder cancer treatment

Summary

Concomitant radiotherapy and cisplatin (CCRT) remains the gold standard in the bladder preservation strategy in case of muscle invasive bladder cancer. We evaluated the role of adding gemcitabine given twice weekly to the standard CCRT. Among patients that received complete treatment, bladder-intact survival was 76% at 5 years and median overall survival was 69.6 months. The maximum-tolerated dose (MTD) of gemcitabine was 25 mg/m².

Bladder preservation and disease control were promising.

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Concomitant treatment with cisplatin and radiotherapy (CCRT) remains the gold standard for bladder preservation in the case of muscle-invasive bladder cancer. We evaluated the benefit of adding gemcitabine given twice a week to the standard CCRT. Among the patients who received the complete treatment, bladder-intact survival was 76% at 5 years and the median overall survival was 69.6 months. The gemcitabine maximum tolerated dose was 25 mg/m². Bladder preservation and disease control were promising.

Abstract

Purpose: Concomitant treatment with radiotherapy and cisplatin (CDDP) remains the gold standard for bladder preservation in the case of muscle-invasive bladder cancer (MIBC). We present the long-term results of a phase I clinical trial to assess the association of twice-weekly gemcitabine with CDDP and radiotherapy in this setting.

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Conclusions: This regimen was well-tolerated. The gemcitabine MTD was 25 mg/m². Bladder preservation and disease control were promising. A multicenter phase II randomized trial is ongoing.

Keywords: bladder cancer; chemo-radiotherapy; gemcitabine; cisplatin; organ preservation

Introduction

Concurrent chemo-radiotherapy (CCRT) for muscle-invasive transitional cell bladder cancer (MIBC) is an acceptable option for patients who are medically unfit for radical surgery as well as for patients initially selected for cystectomy. The standard CCRT includes a cisplatin (CDDP)-containing regimen and is associated with cystectomy-free survival rates between 42% and 55% at 5 years, depending on the initial tumor stage (1-6).

Gemcitabine has been shown to be ~~active-ineffective in treating~~ bladder cancer in combination with CDDP in neoadjuvant and metastatic settings (7, 8). In addition, gemcitabine has significant radiosensitizing activity in various cancer cell lines (9, 10), including those derived from bladder tumors (11). The effectiveness of gemcitabine-based CCRT has been widely reported for many different epithelial tumors (12, 13). Gemcitabine sensitizing activity occurs at sub-cytotoxic doses, and the mechanism involves depletion of the deoxyribonucleoside triphosphate pools, particularly deoxyadenosine triphosphate (dATP) (14). Consecutive studies confirmed that weekly doses ranging from 150 to 450 mg/m² can be successfully used in combination with radiotherapy (10). Furthermore, as preclinical studies showed that even lower doses of gemcitabine effectively radiosensitize cells for up to 72 hours (15, 16), several trials were carried out to test lower gemcitabine doses in clinical settings. Specifically, gemcitabine (twice a week) in combination with radiotherapy (and no CDDP) was well tolerated by patients with MIBC (17). The maximum tolerated dose (MTD) was 27 mg/m² twice a week with 60 Gy delivered to the bladder over 6 weeks.

As the optimal CCRT should contain CDDP, and gemcitabine potentially radiosensitizes bladder cancer cells, we decided to conduct a phase I trial in which patients with initially operable MIBC were treated with gemcitabine twice/week concomitantly with CDDP and radiotherapy.

Methods and Materials

Our local institutional review board approved the protocol, and written informed consent was obtained from all patients. This study was registered at ClinicalTrials.gov, number NCT00556621.

Study design and endpoints

This was a Phase I dose-finding study to determine the MTD and to record acute and late toxicity following CCRT with gemcitabine and CDDP in patients with operable MIBC. The MTD was defined as the gemcitabine dose associated with dose-limiting toxicity (DLT) occurring in 3 out of 6 patients or in 2 out of 3 patients (in this case, an accrual of 3 more patients to the previous dose level was planned).

DLT was defined as: grade 2 or higher pulmonary toxicity, according to the third version of the Common Toxicity Criteria for Adverse Events scale (CTCAE 3.0); all other non-hematological grade 3 or higher CTCAE 3.0 adverse events (except nausea and vomiting); grade 4 thrombocytopenia, grade 3 thrombocytopenia lasting more than seven days or complicated by hemorrhage; grade 4 neutropenia for more than seven days, febrile neutropenia or severe infection.

Patients' selection

Only patients with histologically confirmed MIBC after macroscopically complete transurethral resection of the bladder tumor (TURBT) were enrolled. A second TURBT was carried out if residual microscopic tumor cells were detected around the primary tumor site.

At diagnosis, a CT scan of the chest, abdomen and pelvis and a bone scan were performed to rule out metastatic disease and to stage the tumor in all patients. The pretreatment evaluation included a physical examination and routine laboratory tests, including complete blood cell count, electrolyte, blood urea nitrogen, creatinine and glucose levels and liver function.

Inclusion criteria were: pT2-pT4a MIBC with microscopically complete resection after the first or second TURBT; no macroscopically visible lesions in the pelvic nodes (N0) or distant metastases (M0); absence of carcinoma in situ (CIS); no hydronephrosis; (v) Karnofsky performance score $\geq 70\%$; life expectancy ≥ 6 months; adequate bone marrow reserve (defined as: pretreatment absolute neutrophil count $\geq 1500/\mu\text{L}$, hemoglobin level ≥ 10 g/dL, and platelet count $\geq 100,000/\mu\text{L}$); creatinine clearance ≥ 60 mL/min; bilirubin and AST ≤ 3 and 4 times the institutional upper limits of normal, respectively); age ≥ 18 years; signed informed consent form.

Pregnant or breast-feeding patients were excluded as well as patients with previous radiotherapy or chemotherapy treatments (except anterior intra-bladder treatment for localized CIS), or history of malignancies other than adequately treated basal cell or squamous cell skin cancer or in situ cervical carcinoma.

Treatment plan

The treatment was started within eight weeks after complete TURBT.

Radiotherapy

Patients underwent CT-based virtual simulation using 2.5 mm thick slices obtained at 2.5 mm intervals. Patients were treated in a supine position with empty bladder.

During the first CCRT part a fractionated dose of 45 Gy (1.8 Gy/fraction/day in 25 fractions, over five weeks) was administered to the small pelvis (from S1-S2 to the obturator foramen or

the ischiatic tuberosity in case of bladder neck or prostatic urethra invasion) using a 4-field box technique. The clinical target volume included the bladder, the obturators and the internal and external iliac lymph nodes. During the second CCRT part, 18 Gy (1.8 Gy/fraction/day in 10 fractions, over two weeks) were delivered to a clinical target volume limited to the initial tumor volume, using reduced-box or opposed lateral or antero-posterior fields. A 1.5-cm margin was added to the clinical target volume to allow for geometric uncertainties (planning target volume).

Patients were treated with 18 MV photon beams. Dose prescription was in accordance with the ICRU 62 report for each patient.

Cisplatin (CDDP)

CDDP was given at a dose of 20 mg/m²/day by continuous ~~intravenous-v-~~ infusion during 4 consecutive days (from day 2 to day 5 and from day 23 to day 26 during the first CCRT part and from day 2 to 5 of the second CCRT part). Patients were hydrated and received anti-emetic drugs according to our in-house protocol.

Gemcitabine

Gemcitabine was administered intravenously in 50–100 mL of normal saline over 30 min 2 to 6 hours prior to irradiation and two times a week, on day 2, 5, 9, 12, 16, 19, 23, 26, 30 and 33 (first CCRT part) and on day 2, 5, 9 and 12 (second CCRT part).

The starting gemcitabine dose was 15 mg/m² twice/week with planned dose escalation of 5 mg/m² every two weeks unless the MTD was reached. Dose escalation was not allowed in the same patient.

Dose modification

Dose adjustments were based on the weekly absolute neutrophil count (ANC) and platelet count, assessed no later than 36 hours before the gemcitabine infusion and on the clinical assessment of non-hematological toxicities. Gemcitabine dose was not modified if the ANC was $> 1000/\mu\text{L}$ and/or the platelet count was $> 100,000/\mu\text{L}$. In the case of an ANC between 500 and $1000/\mu\text{L}$ and a platelet count between 50,000 and $100,000/\mu\text{L}$, gemcitabine was not administered. In the case of an even lower ANC or platelet count, chemotherapy was definitively stopped.

Reduction of the creatinine clearance level between 40 and 60 mL/min entailed a 50% decrease of the CDDP dose. In the case of even lower values, CDDP was stopped for the entire course.

If a DLT occurred, chemotherapy was stopped, but radiotherapy could be continued based on the investigator's assessment.

Follow-up, toxicity and response evaluation

During treatment, patients were seen weekly at the Radiation Oncology Department and weight, toxicity and complete blood count (including blood cell differential and platelet count twice a week before each gemcitabine injection) were recorded.

An evaluation by cystoscopy and TURBT under general anesthesia was performed during the third week after the end of the first CCRT part. Complete response (CR) was defined as the absence of any macroscopic or microscopic lesion confirmed by the pathologist. In the case of residual disease, total cystectomy was proposed to the patient. In the case of CR, the second CCRT part was started as soon as possible and no later than four weeks from the completion of the first cycle. The final evaluation was done by cystoscopy and TURBT six to eight weeks after CCRT completion.

After the end of the treatment, patients were clinically assessed every month for the first four months and then once every six months (clinical examination, CT scan with contrast and cystoscopy).

Statistical analysis

Data were analyzed using the STATA software version 8.0 (Stata Corporation, College Station, TX, USA). Survival probabilities were estimated using the actuarial or the Kaplan-Meier method and the following definitions.

Overall survival (OS): the event was death from any cause. The time to OS was the interval between treatment initiation and death, or the most recent follow-up if no event occurred.

Disease-specific survival (DSS): the event was death attributable to bladder cancer. The time to DSS was the interval between treatment initiation and death from bladder cancer, or the most recent follow-up if no event occurred.

Bladder-intact survival (BIS): the event was cystectomy for any reason or death from any cause. The time to BIS was the interval between treatment initiation and cystectomy or death (whichever was shorter), or the most recent follow-up if no event occurred.

Results

Patients' characteristics and response to treatment

Fourteen patients with a median age of 72 years (range 51-83) were included in this study between June 2005 and June 2009. The patients' characteristics are listed in Table 1.

One patient was excluded from the protocol on day 5 of the first CCRT cycle due to poor compliance (intravenous drip pulled out and aggressive behavior). He was then treated off-protocol with radiotherapy (total dose: 63 Gy; complete response after the first cycle) and CDDP alone (modified dose of 40 mg/m²/day on day 23 and 24 of the first cycle and on day 2 and 3 of the second cycle). He was included in the follow-up assessment ("intent-to-treat" approach).

All patients received the first radiotherapy part (45 Gy) and 12 patients (86%) completed the whole radiotherapy protocol (45 Gy + 18 Gy). Nine patients (64%) completed the whole CCRT course with gemcitabine and CDDP.

At the TURBT evaluation after the first CCRT part, ten patients showed CR (71% of the included patients). One patient had stable disease and underwent cystectomy. Two patients (14%) had progressive disease: one underwent cystectomy and the other (who refused radical surgery) continued with the second CCRT part with CR at the end of the treatment. One patient (7%) could not be evaluated (excluded from the protocol).

The intact bladder preservation rate was 86% for all included patients (12 out of 14 patients).

Toxicity

Table 2 reports the acute adverse events that occurred outside the radiation field and could thus be considered as related to chemotherapy. They were mainly hematological disorders,

digestive alterations and asthenia. Only two of these adverse events were considered as-DLT (grade 4 thrombocytopenia and grade 3 asthenia). Table 3 reports the adverse events due to radiotherapy in the 14 patients. As expected, urinary discomfort and diarrhea were the two main acute adverse events. No in-field severe events (to be considered as DLT) were observed. Table 4 details the gemcitabine dose, the time of appearance of toxicity, the toxicity grade and DLT leading to chemotherapy delay. DLT was confirmed in two patients. One was a grade 4 thrombocytopenia at day 16 after four injections of 30 mg/m² gemcitabine and one 4-day continuous infusion of CDDP. Chemotherapy was stopped, and the patient spontaneously recovered. CR was achieved after radiotherapy alone. The second DLT occurred at day 26 and consisted of an overall alteration of the performance status, arrhythmia (auricular fibrillation) and global edema. The patient had already received eight injections of 30 mg/m² gemcitabine and two 4-day continuous infusions of CDDP. Only radiotherapy was continued and CR was achieved.

Follow-up and survival

The median follow-up was 53 months (4.4 years) for the whole cohort. Two patients died of progressive metastatic disease. One died of metastatic disease after salvage cystectomy for progressive local disease during the first CCRT part. The second one died of metastatic disease in the first year although the tumor was locally controlled.

Four patients died of undercurrent diseases. One patient died of an ischemic stroke after treatment completion, another of metastatic breast disease and the other two from cardiovascular disease.

The median OS for all patients was 5.8 years. The actuarial OS rates were 79% (at 2 years), 71% (3 years) and 62% (5 years). The median DSS was not reached, but the actuarial DSS

rate was 77% at five years. The median BIS was 5.8 years for all patients. The actuarial BIS rates were 64% at three years and 56% at five years (Fig.1).

The nine patients who received the whole CCRT protocol had a median OS of 5.8 years, a 5-year actuarial DSS rate of 89% and SIB of 89% (at three years) and 76% (five years).

No salvage cystectomy for local tumor recurrence or toxicity was performed during the follow-up period and no significant long-term late toxicity occurred during the follow-up.

Discussion

CCRT with CDDP is the most studied protocol for the conservative management of MIBC. Although other systemic drugs (such as 5-FU, taxanes, or gemcitabine) have been already added to CDDP to increase local control, the combination of fractionated pelvic radiotherapy, CDDP and gemcitabine administered twice weekly ~~was~~has never been tested~~before~~.

We present here the long-term results of our phase I study to assess gemcitabine as a potent radiosensitizer in combination with CDDP for the conservative management of MIBC. A standard 3+3 Phase I dose escalation schedule was planned as no data was available on the twice-weekly gemcitabine and CDDP combination as radiosensitizers. A long-term follow-up of our patients was required as gemcitabine may potentially increase late toxicity, when combined with pelvic radiotherapy. However, the observed toxicity was acceptable with just one grade four thrombocytopenia and one grade four asthenia considered as DLT. No in-field severe event occurred. Regarding the efficacy, our long-term results are quite similar to previously published data in this setting (18, 19). Indeed, among patients that received the complete treatment, BIS was 76% at five years and the median OS was 69.6 months.

Another phase I trial combining gemcitabine and RT with long-term results has been already published, but the pelvic fields were not treated thus making difficult any comparison (20). As usually performed, especially in the trials of the Radiation Therapy Oncology Group (21), we included the pelvic lymph nodes in the radiation field because lymph node involvement is about 20% and 40% in pT2 and pT3 tumors, respectively (22). Another phase I study including pelvic fields with gemcitabine reported high toxicity rates and had to be amended to a de-escalation study, with a 25 mg/m² decrease at each level (23). Consequently, the toxicity observed in this phase I trial should absolutely be interpreted by taking into account this large radiation volume that increases the risk of interactions between ionizing radiation, gemcitabine and CDDP.

Kent et al. conducted a phase I study on gemcitabine given twice weekly without CDDP and with 60 Gy of radiation after TURBT (17). DLT included deep venous thrombosis, diarrhea, abnormal liver function tests and edema. The recommended dose in this trial was 27 mg/m² twice-weekly, which is close to the MTD found in our study (25 mg/m² given twice-weekly).

Besides, Caffo et al. performed a phase I study on conservative radiotherapy with weekly gemcitabine and 100 mg/m² CDDP every three weeks (18). Starting with 200 mg/m²/week gemcitabine, they escalated the dose up to 500 mg/m²/week, with two DLT: one death and one intestinal perforation. The gemcitabine recommended dose of 400 mg/m²/week was then evaluated in a phase II study that was unfortunately prematurely closed due to low accrual. The radiotherapy dose was 54 Gy (1.8 Gy/fraction) in both trials. A pooled analysis of the two trials on 26 patients was published in 2010 with a median follow-up of 74 months (24). The 5-year clinical outcomes were a 70.1% OS rate, a 78.9% DSS rate and a 73.8% BIS rate. Although this association was effective as all evaluable patients were disease-free at the time of the cystoscopic evaluation, concerns regarding toxicity with the weekly gemcitabine schedule remain. Indeed, intestinal toxicities in the phase I study and neutropenia in the phase II study frequently occurred (even after omission of the gemcitabine injection at day 15 and 36) and for that reason we chose a twice-weekly schedule allowing for lower doses of gemcitabine.

In our study, we used standard radiotherapy fractionation (1.8 Gy/fraction/day 5 days a week). However, another group studied gemcitabine radiosensitization with hypofractionated chemoradiotherapy (52.5 Gy in 20 fractions over 28 days) in a phase I study and found a MTD of 100 mg/m² when delivered only once a week and without CDDP (25). The consecutive phase II trial included 50 patients with transitional cell carcinoma staged T2-3 N0 M0 (19). All patients completed the radiotherapy course; 46 (92%) tolerated all four gemcitabine cycles. Two patients stopped after two cycles, and two after three cycles, due to bowel toxicity. Forty-four (88%) achieved a complete endoscopic response. At a median follow-up of 36

months (range, 15- 62 months), 36 patients were alive and 32 had a functional and intact bladder. By using Kaplan-Meier analyses, the 3-year cancer-specific survival was 82%, and OS was 75%. Nevertheless, these results were obtained with hypofractionated conformal radiotherapy that used a four-field plan with multi-leaf collimators, delivered to the whole bladder and a minimum 1.5-cm margin. Finally, these regimens are clearly manageable for patients with comorbidities but we are still convinced that CDDP presents a strong added-value in fit patients.

The results presented here allowed us to determine the gemcitabine MTD when given twice a week in combination with CDDP and radiotherapy. Although bladder preservation and disease control results are promising, this remains a phase I study with only 14 patients and a further validation in a larger cohort is needed. In view of these findings, a French phase II randomized multi-institutional trial named GETUG V04 started in 2011 to assess the efficacy and tolerability of this new combination strategy with gemcitabine twice-weekly compared to the standard CCRT schedule with CDDP alone (NCT01495676).

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Figure legends

Fig. 1 Survival curves obtained using the Kaplan-Meier method for the overall survival (OS), disease-specific survival (DSS) and bladder-intact survival (BIS).

Combined Chemo-radiotherapy with Twice-weekly Gemcitabine and Cisplatin for Organ Preservation in Muscle-invasive Bladder Cancer: Long-term Results of a Phase I Trial

Running title: Conservative bladder cancer treatment

Summary

Concomitant treatment with cisplatin and radiotherapy (CCRT) remains the gold standard for bladder preservation in the case of muscle-invasive bladder cancer. We evaluated the benefit of adding gemcitabine given twice a week to the standard CCRT. Among the patients who received the complete treatment, bladder-intact survival was 76% at 5 years and the median overall survival was 69.6 months. The gemcitabine maximum tolerated dose was 25 mg/m². Bladder preservation and disease control were promising.

Abstract

Purpose: Concomitant treatment with radiotherapy and cisplatin (CDDP) remains the gold standard for bladder preservation in the case of muscle-invasive bladder cancer (MIBC). We present the long-term results of a phase I clinical trial to assess the association of twice-weekly gemcitabine with CDDP and radiotherapy in this setting.

Methods and Materials: Patients with pT2-pT4 N0 M0 MIBC without hydronephrosis or diffuse carcinoma in situ were enrolled in this study. After maximal transurethral resection of the bladder tumor, patients received concomitantly radiotherapy (63 Gy in 1.8 fractions) and chemotherapy (20 mg CDDP /m²/day over 4 days every 21 days; and gemcitabine twice a week). The starting dose of gemcitabine was 15 mg/m² with dose escalation to 20, 25 and 30

mg/m². The primary endpoint was the maximum tolerated dose (MTD). Secondary endpoints included toxicity and tumor control.

Results: Fourteen patients were enrolled. Dose-limiting toxicity (DLT) occurred in two patients treated with 30 mg/m² gemcitabine (grade 4 thrombocytopenia and severe impairment of the WHO performance status, respectively). Nine patients received the complete chemo-radiotherapy protocol. The recommended dose of gemcitabine was 25 mg/m². The median follow-up was 53 months, and the overall and disease-specific 5-year survival rates were 62% and 77%, respectively. Among the patients who received the complete treatment, bladder-intact survival was 76% at 5 years and the median overall survival was 69.6 months.

Conclusions: This regimen was well-tolerated. The gemcitabine MTD was 25 mg/m². Bladder preservation and disease control were promising. A multicenter phase II randomized trial is ongoing.

Keywords: bladder cancer; chemo-radiotherapy; gemcitabine; cisplatin; organ preservation

Introduction

Concurrent chemo-radiotherapy (CCRT) for muscle-invasive transitional cell bladder cancer (MIBC) is an acceptable option for patients who are medically unfit for radical surgery as well as for patients initially selected for cystectomy. The standard CCRT includes a cisplatin (CDDP)-containing regimen and is associated with cystectomy-free survival rates between 42% and 55% at 5 years, depending on the initial tumor stage (1-6).

Gemcitabine has been shown to be effective in treating bladder cancer in combination with CDDP in neoadjuvant and metastatic settings (7, 8). In addition, gemcitabine has significant radiosensitizing activity in various cancer cell lines (9, 10), including those derived from bladder tumors (11). The effectiveness of gemcitabine-based CCRT has been widely reported for many different epithelial tumors (12, 13). Gemcitabine sensitizing activity occurs at sub-cytotoxic doses, and the mechanism involves depletion of the deoxyribonucleoside triphosphate pools, particularly deoxyadenosine triphosphate (dATP) (14). Consecutive studies confirmed that weekly doses ranging from 150 to 450 mg/m² can be successfully used in combination with radiotherapy (10). Furthermore, as preclinical studies showed that even lower doses of gemcitabine effectively radiosensitize cells for up to 72 hours (15, 16), several trials were carried out to test lower gemcitabine doses in clinical settings. Specifically, gemcitabine (twice a week) in combination with radiotherapy (and no CDDP) was well tolerated by patients with MIBC (17). The maximum tolerated dose (MTD) was 27 mg/m² twice a week with 60 Gy delivered to the bladder over 6 weeks.

As the optimal CCRT should contain CDDP, and gemcitabine potentially radiosensitizes bladder cancer cells, we decided to conduct a phase I trial in which patients with initially operable MIBC were treated with gemcitabine twice/week concomitantly with CDDP and radiotherapy.

Methods and Materials

Our local institutional review board approved the protocol, and written informed consent was obtained from all patients. This study was registered at ClinicalTrials.gov, number NCT00556621.

Study design and endpoints

This was a Phase I dose-finding study to determine the MTD and to record acute and late toxicity following CCRT with gemcitabine and CDDP in patients with operable MIBC. The MTD was defined as the gemcitabine dose associated with dose-limiting toxicity (DLT) occurring in 3 out of 6 patients or in 2 out of 3 patients (in this case, an accrual of 3 more patients to the previous dose level was planned).

DLT was defined as: grade 2 or higher pulmonary toxicity, according to the third version of the Common Toxicity Criteria for Adverse Events scale (CTCAE 3.0); all other non-hematological grade 3 or higher CTCAE 3.0 adverse events (except nausea and vomiting); grade 4 thrombocytopenia, grade 3 thrombocytopenia lasting more than seven days or complicated by hemorrhage; grade 4 neutropenia for more than seven days, febrile neutropenia or severe infection.

Patient selection

Only patients with histologically confirmed MIBC after macroscopically complete transurethral resection of the bladder tumor (TURBT) were enrolled. A second TURBT was carried out if residual microscopic tumor cells were detected around the primary tumor site.

At diagnosis, a CT scan of the chest, abdomen and pelvis and a bone scan were performed to rule out metastatic disease and to stage the tumor in all patients. The pretreatment evaluation included a physical examination and routine laboratory tests, including complete blood cell count, electrolyte, blood urea nitrogen, creatinine and glucose levels and liver function.

Inclusion criteria were: pT2-pT4a MIBC with microscopically complete resection after the first or second TURBT; no macroscopically visible lesions in the pelvic nodes (N0) or distant metastases (M0); absence of carcinoma in situ (CIS); no hydronephrosis; (v) Karnofsky performance score $\geq 70\%$; life expectancy ≥ 6 months; adequate bone marrow reserve (defined as: pretreatment absolute neutrophil count $\geq 1500/\mu\text{L}$, hemoglobin level ≥ 10 g/dL, and platelet count $\geq 100,000/\mu\text{L}$); creatinine clearance ≥ 60 mL/min; bilirubin and AST ≤ 3 and 4 times the institutional upper limits of normal, respectively); age ≥ 18 years; signed informed consent form.

Pregnant or breast-feeding patients were excluded as well as patients with previous radiotherapy or chemotherapy treatments (except anterior intra-bladder treatment for localized CIS), or history of malignancies other than adequately treated basal cell or squamous cell skin cancer or in situ cervical carcinoma.

Treatment plan

The treatment was started within eight weeks after complete TURBT.

Radiotherapy

Patients underwent CT-based virtual simulation using 2.5 mm thick slices obtained at 2.5 mm intervals. Patients were treated in a supine position with empty bladder.

During the first CCRT part a fractionated dose of 45 Gy (1.8 Gy/fraction/day in 25 fractions, over five weeks) was administered to the small pelvis (from S1-S2 to the obturator foramen or

the ischiatic tuberosity in case of bladder neck or prostatic urethra invasion) using a 4-field box technique. The clinical target volume included the bladder, the obturators and the internal and external iliac lymph nodes. During the second CCRT part, 18 Gy (1.8 Gy/fraction/day in 10 fractions, over two weeks) were delivered to a clinical target volume limited to the initial tumor volume, using reduced-box or opposed lateral or antero-posterior fields. A 1.5-cm margin was added to the clinical target volume to allow for geometric uncertainties (planning target volume).

Patients were treated with 18 MV photon beams. Dose prescription was in accordance with the ICRU 62 report for each patient.

Cisplatin (CDDP)

CDDP was given at a dose of 20 mg/m²/day by continuous intravenous infusion during 4 consecutive days (from day 2 to day 5 and from day 23 to day 26 during the first CCRT part and from day 2 to 5 of the second CCRT part). Patients were hydrated and received anti-emetic drugs according to our in-house protocol.

Gemcitabine

Gemcitabine was administered intravenously in 50–100 mL of normal saline over 30 min 2 to 6 hours prior to irradiation and two times a week, on day 2, 5, 9, 12, 16, 19, 23, 26, 30 and 33 (first CCRT part) and on day 2, 5, 9 and 12 (second CCRT part).

The starting gemcitabine dose was 15 mg/m² twice/week with planned dose escalation of 5 mg/m² every two weeks unless the MTD was reached. Dose escalation was not allowed in the same patient.

Dose modification

Dose adjustments were based on the weekly absolute neutrophil count (ANC) and platelet count, assessed no later than 36 hours before the gemcitabine infusion and on the clinical assessment of non-hematological toxicities. Gemcitabine dose was not modified if the ANC was $> 1000/\mu\text{L}$ and/or the platelet count was $> 100,000/\mu\text{L}$. In the case of an ANC between 500 and $1000/\mu\text{L}$ and a platelet count between 50,000 and $100,000/\mu\text{L}$, gemcitabine was not administered. In the case of an even lower ANC or platelet count, chemotherapy was definitively stopped.

Reduction of the creatinine clearance level between 40 and 60 mL/min entailed a 50% decrease of the CDDP dose. In the case of even lower values, CDDP was stopped for the entire course.

If a DLT occurred, chemotherapy was stopped, but radiotherapy could be continued based on the investigator's assessment.

Follow-up, toxicity and response evaluation

During treatment, patients were seen weekly at the Radiation Oncology Department and weight, toxicity and complete blood count (including blood cell differential and platelet count twice a week before each gemcitabine injection) were recorded.

An evaluation by cystoscopy and TURBT under general anesthesia was performed during the third week after the end of the first CCRT part. Complete response (CR) was defined as the absence of any macroscopic or microscopic lesion confirmed by the pathologist. In the case of residual disease, total cystectomy was proposed to the patient. In the case of CR, the second CCRT part was started as soon as possible and no later than four weeks from the completion of the first cycle. The final evaluation was done by cystoscopy and TURBT six to eight weeks after CCRT completion.

After the end of the treatment, patients were clinically assessed every month for the first four months and then once every six months (clinical examination, CT scan with contrast and cystoscopy).

Statistical analysis

Data were analyzed using the STATA software version 8.0 (Stata Corporation, College Station, TX, USA). Survival probabilities were estimated using the actuarial or the Kaplan-Meier method and the following definitions.

Overall survival (OS): the event was death from any cause. The time to OS was the interval between treatment initiation and death, or the most recent follow-up if no event occurred.

Disease-specific survival (DSS): the event was death attributable to bladder cancer. The time to DSS was the interval between treatment initiation and death from bladder cancer, or the most recent follow-up if no event occurred.

Bladder-intact survival (BIS): the event was cystectomy for any reason or death from any cause. The time to BIS was the interval between treatment initiation and cystectomy or death (whichever was shorter), or the most recent follow-up if no event occurred.

Results

Patients' characteristics and response to treatment

Fourteen patients with a median age of 72 years (range 51-83) were included in this study between June 2005 and June 2009. The patients' characteristics are listed in Table 1.

One patient was excluded from the protocol on day 5 of the first CCRT cycle due to poor compliance (intravenous drip pulled out and aggressive behavior). He was then treated off-protocol with radiotherapy (total dose: 63 Gy; complete response after the first cycle) and CDDP alone (modified dose of 40 mg/m²/day on day 23 and 24 of the first cycle and on day 2 and 3 of the second cycle). He was included in the follow-up assessment ("intent-to-treat" approach).

All patients received the first radiotherapy part (45 Gy) and 12 patients (86%) completed the whole radiotherapy protocol (45 Gy + 18 Gy). Nine patients (64%) completed the whole CCRT course with gemcitabine and CDDP.

At the TURBT evaluation after the first CCRT part, ten patients showed CR (71% of the included patients). One patient had stable disease and underwent cystectomy. Two patients (14%) had progressive disease: one underwent cystectomy and the other (who refused radical surgery) continued with the second CCRT part with CR at the end of the treatment. One patient (7%) could not be evaluated (excluded from the protocol).

The intact bladder preservation rate was 86% for all included patients (12 out of 14 patients).

Toxicity

Table 2 reports the acute adverse events that occurred outside the radiation field and could thus be considered as related to chemotherapy. They were mainly hematological disorders,

digestive alterations and asthenia. Only two of these adverse events were considered DLT (grade 4 thrombocytopenia and grade 3 asthenia). Table 3 reports the adverse events due to radiotherapy in the 14 patients. As expected, urinary discomfort and diarrhea were the two main acute adverse events. No in-field severe events (to be considered as DLT) were observed. Table 4 details the gemcitabine dose, the time of appearance of toxicity, the toxicity grade and DLT leading to chemotherapy delay. DLT was confirmed in two patients. One was a grade 4 thrombocytopenia at day 16 after four injections of 30 mg/m² gemcitabine and one 4-day continuous infusion of CDDP. Chemotherapy was stopped, and the patient spontaneously recovered. CR was achieved after radiotherapy alone. The second DLT occurred at day 26 and consisted of an overall alteration of the performance status, arrhythmia (auricular fibrillation) and global edema. The patient had already received eight injections of 30 mg/m² gemcitabine and two 4-day continuous infusions of CDDP. Only radiotherapy was continued and CR was achieved.

Follow-up and survival

The median follow-up was 53 months (4.4 years) for the whole cohort. Two patients died of progressive metastatic disease. One died of metastatic disease after salvage cystectomy for progressive local disease during the first CCRT part. The second one died of metastatic disease in the first year although the tumor was locally controlled.

Four patients died of undercurrent diseases. One patient died of an ischemic stroke after treatment completion, another of metastatic breast disease and the other two from cardiovascular disease.

The median OS for all patients was 5.8 years. The actuarial OS rates were 79% (at 2 years), 71% (3 years) and 62% (5 years). The median DSS was not reached, but the actuarial DSS

rate was 77% at five years. The median BIS was 5.8 years for all patients. The actuarial BIS rates were 64% at three years and 56% at five years (Fig.1).

The nine patients who received the whole CCRT protocol had a median OS of 5.8 years, a 5-year actuarial DSS rate of 89% and SIB of 89% (at three years) and 76% (five years).

No salvage cystectomy for local tumor recurrence or toxicity was performed during the follow-up period and no significant long-term late toxicity occurred during the follow-up.

Discussion

CCRT with CDDP is the most studied protocol for the conservative management of MIBC. Although other systemic drugs (such as 5-FU, taxanes, or gemcitabine) have been already added to CDDP to increase local control, the combination of fractionated pelvic radiotherapy, CDDP and gemcitabine administered twice weekly has never been tested.

We present here the long-term results of our phase I study to assess gemcitabine as a potent radiosensitizer in combination with CDDP for the conservative management of MIBC. A standard 3+3 Phase I dose escalation schedule was planned as no data was available on the twice-weekly gemcitabine and CDDP combination as radiosensitizers. A long-term follow-up of our patients was required as gemcitabine may potentially increase late toxicity, when combined with pelvic radiotherapy. However, the observed toxicity was acceptable with just one grade four thrombocytopenia and one grade four asthenia considered as DLT. No in-field severe event occurred. Regarding the efficacy, our long-term results are quite similar to previously published data in this setting (18, 19). Indeed, among patients that received the complete treatment, BIS was 76% at five years and the median OS was 69.6 months.

Another phase I trial combining gemcitabine and RT with long-term results has been already published, but the pelvic fields were not treated thus making difficult any comparison (20). As usually performed, especially in the trials of the Radiation Therapy Oncology Group (21), we included the pelvic lymph nodes in the radiation field because lymph node involvement is about 20% and 40% in pT2 and pT3 tumors, respectively (22). Another phase I study including pelvic fields with gemcitabine reported high toxicity rates and had to be amended to a de-escalation study, with a 25 mg/m² decrease at each level (23). Consequently, the toxicity observed in this phase I trial should absolutely be interpreted by taking into account this large radiation volume that increases the risk of interactions between ionizing radiation, gemcitabine and CDDP.

Kent et al. conducted a phase I study on gemcitabine given twice weekly without CDDP and with 60 Gy of radiation after TURBT (17). DLT included deep venous thrombosis, diarrhea, abnormal liver function tests and edema. The recommended dose in this trial was 27 mg/m² twice-weekly, which is close to the MTD found in our study (25 mg/m² given twice-weekly).

Caffo et al. performed a phase I study on conservative radiotherapy with weekly gemcitabine and 100 mg/m² CDDP every three weeks (18). Starting with 200 mg/m²/week gemcitabine, they escalated the dose up to 500 mg/m²/week, with two DLT: one death and one intestinal perforation. The gemcitabine recommended dose of 400 mg/m²/week was then evaluated in a phase II study that was unfortunately prematurely closed due to low accrual. The radiotherapy dose was 54 Gy (1.8 Gy/fraction) in both trials. A pooled analysis of the two trials on 26 patients was published in 2010 with a median follow-up of 74 months (24). The 5-year clinical outcomes were a 70.1% OS rate, a 78.9% DSS rate and a 73.8% BIS rate. Although this association was effective as all evaluable patients were disease-free at the time of the cystoscopic evaluation, concerns regarding toxicity with the weekly gemcitabine schedule remain. Indeed, intestinal toxicities in the phase I study and neutropenia in the phase II study frequently occurred (even after omission of the gemcitabine injection at day 15 and 36) and for that reason we chose a twice-weekly schedule allowing for lower doses of gemcitabine.

In our study, we used standard radiotherapy fractionation (1.8 Gy/fraction/day 5 days a week). However, another group studied gemcitabine radiosensitization with hypofractionated chemoradiotherapy (52.5 Gy in 20 fractions over 28 days) in a phase I study and found a MTD of 100 mg/m² when delivered only once a week and without CDDP (25). The consecutive phase II trial included 50 patients with transitional cell carcinoma staged T2-3 N0 M0 (19). All patients completed the radiotherapy course; 46 (92%) tolerated all four gemcitabine cycles. Two patients stopped after two cycles, and two after three cycles, due to bowel toxicity. Forty-four (88%) achieved a complete endoscopic response. At a median follow-up of 36 months (range, 15- 62 months), 36 patients were alive and 32 had a functional and intact

bladder. By using Kaplan-Meier analyses, the 3-year cancer-specific survival was 82%, and OS was 75%. Nevertheless, these results were obtained with hypofractionated conformal radiotherapy that used a four-field plan with multi-leaf collimators, delivered to the whole bladder and a minimum 1.5-cm margin. Finally, these regimens are clearly manageable for patients with comorbidities but we are still convinced that CDDP presents a strong added-value in fit patients.

The results presented here allowed us to determine the gemcitabine MTD when given twice a week in combination with CDDP and radiotherapy. Although bladder preservation and disease control results are promising, this remains a phase I study with only 14 patients and a further validation in a larger cohort is needed. In view of these findings, a French phase II randomized multi-institutional trial named GETUG V04 started in 2011 to assess the efficacy and tolerability of this new combination strategy with gemcitabine twice-weekly compared to the standard CCRT schedule with CDDP alone (NCT01495676).

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Figure legends

Fig. 1 Survival curves obtained using the Kaplan-Meier method for the overall survival (OS), disease-specific survival (DSS) and bladder-intact survival (BIS).

Table 1 Patient characteristics

Characteristic	n (%)
Sex	
male	11 (79)
female	3 (21)
Age	
median	72
range	51-83
Histologic grade	
poorly differentiated	10 (71)
moderately differentiated	3 (21)
unknown	1 (7)
TNM stage	
T2	12 (86)
T4	2 (14)
N0	14 (100)
M0	14 (100)
Gemcitabine biweekly dose (mg/m ²)	
15	3 (21)
20	3 (21)
25	6 (43)
30	2 (14)

Table 2 Acute adverse events occurring outside the radiation fields

Toxicity type	Grade 0, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Thrombopenia	1 (7.1)	7 (50)	4 (28.6)	1 (7.1)	1 (7.1)
Neutropenia	5 (35.7)	3 (21.4)	2 (14.3)	4 (28.6)	0 (0)
Anemia	5 (35.7)	7 (50)	2 (14.3)	0 (0)	0 (0)
Infection	12 (85.7)	1 (7.1)	1 (7.1)	0 (0)	0 (0)
Renal	12 (85.7)	1 (7.1)	1 (7.1)	0 (0)	0 (0)
Pulmonary	12 (85.7)	1 (7.1)	1 (7.1)	0 (0)	0 (0)
Fever	12 (85.7)	0 (0)	2 (14.3)	0 (0)	0 (0)
Nausea	6 (42.9)	7 (50)	0 (0)	1 (7.1)	0 (0)
Vomiting	11 (78.6)	1 (7.1)	2 (14.3)	0 (0)	0 (0)
Dyspnea	13 (92.9)	1 (7.1)	0 (0)	0 (0)	0 (0)
Asthenia	3 (21.4)	6 (42.9)	4 (28.6)	1 (7.1)	0 (0)
Insomnia	13 (92.9)	1 (7.1)	0 (0)	0 (0)	0 (0)
Anorexia	12 (85.7)	1 (7.1)	1 (7.1)	0 (0)	0 (0)
Hepatic	12 (85.7)	0 (0)	2 (14.3)	0 (0)	0 (0)
Cutaneous	13 (92.9)	1 (7.1)	0 (0)	0 (0)	0 (0)
Auditive	14 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Neurologic	14 (100)	0 (0)	0 (0)	0 (0)	0 (0)

Table 3 Acute adverse events occurring within the radiation fields

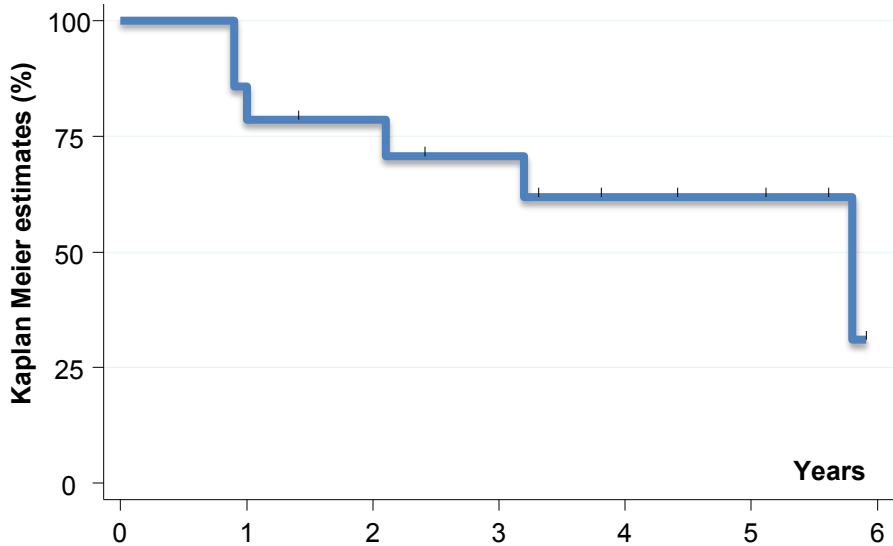
Toxicity type	Grade 0, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Urinary incontinence	11 (78.6)	2 (15.4)	1 (7.1)	0 (0)	0 (0)
Urination retention	13 (92.9)	0 (0)	1 (7.1)	0 (0)	0 (0)
Hematuria	12 (85.7)	1 (7.1)	0 (0)	0 (0)	0 (0)
Dysuria	11 (78.6)	3 (21.4)	0 (0)	0 (0)	0 (0)
Pollakiuria	13 (92.9)	0 (0)	1 (7.1)	0 (0)	0 (0)
Diarrhea	9 (64.3)	2 (15.4)	3 (21.4)	0 (0)	0 (0)
Dyserection	10 (90.9)	0 (0)	1 (9.1)	0 (0)	0 (0)
Cutaneous	13 (92.9)	1 (7.1)	0 (0)	0 (0)	0 (0)

Table 4 Toxicity appearance time and dose-limiting toxicity (DLT) confirmation

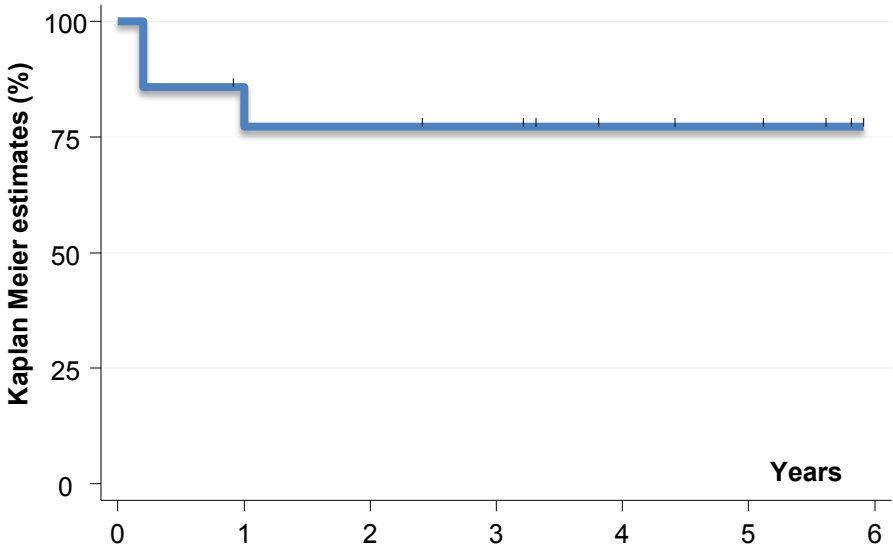
Patient number	Biweekly gemcitabine dose	Day since treatment initiation	Toxicity grade	Toxicity type	Dose-limiting toxicity
1	15	23	3	neutropenia	No
2	15	16	1	thrombopenia	No
2	15	19	1	thrombopenia	No
4	20	23	3	neutropenia	No
5	20	16	2	thrombopenia	No
6	20	12	2	infection	No
6	20	16	2	infection	No
6	20	19	2	infection	No
9	25	12	1	thrombopenia	No
9	25	16	2	thrombopenia	No
9	25	19	1	thrombopenia	No
9	25	33	1	thrombopenia	No
10	30	16	4	thrombopenia	Yes
11	30	26	3	asthenia	Yes
12	25	16	3	thrombopenia	No
12	25	19	2	thrombopenia	No
12	25	23	1	thrombopenia	No
12	25	26	1	thrombopenia	No
12	25	30	1	thrombopenia	No
12	25	33	1	thrombopenia	No
13	25	23	2	neutropenia	No
13	25	26	2	neutropenia	No
14	25	16	2	thrombopenia	No
14	25	19	2	thrombopenia	No

Figure 1
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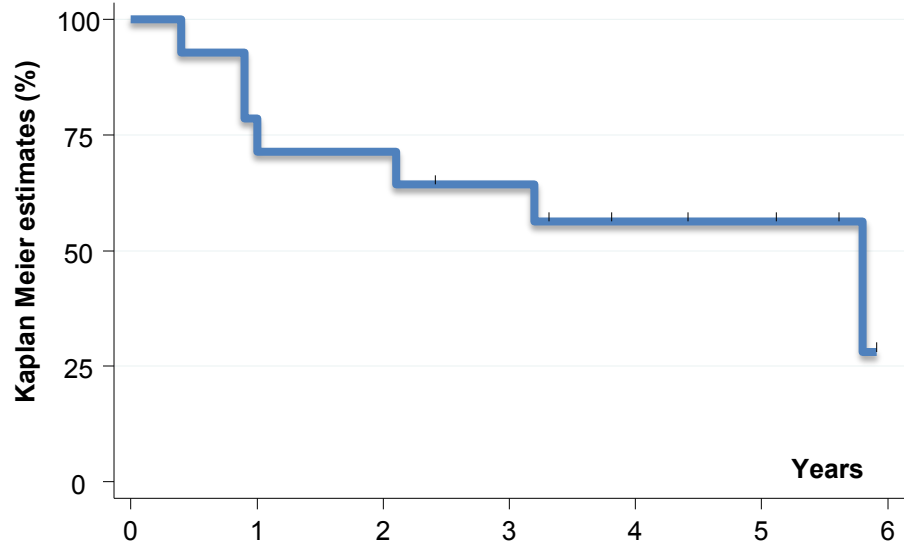
Overall Survival



Progression-Free Survival



Bladder-intact Survival



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