A Study of Adjuvant vs. Progression-Triggered Treatment with Gemcitabine after Radical Cystectomy for Locally Advanced Transitional Cell Carcinoma of the Bladder in Patients not Suitable for Cisplatin-based Chemotherapy - a Randomized Phase 3 Study

Principal Investigator:
Michael Stöckle M.D., Professor of Urology
Department of Urology
Universität des Saarlandes
Kirrberger Strasse
D-66421 Homburg/Saar

Phone: 0049-6841-1624702
Fax: 0049-6841-1624795

Statistician:
Stefan Wellek, Ph.D., Professor of Biostatistics
University of Heidelberg
Division of Biostatistics,
Center of Mental Health Mannheim
Postfach 12 21 20
D-68072 Mannheim

Phone: 0049-621-1703714
Fax: 0049-621-23429

Study Coordinators:
Jan Lehmann, MD
Department of Urology
Universität des Saarlandes
Kirrberger Strasse
D-66421 Homburg/Saar

Phone: 0049-6841-1624700
Fax: 0049-6841-172353

Markus Müller, MD
Department of Urology
Universitätsklinikum Benjamin-Franklin
Hindenburgdamm 30
D-12200 Berlin

Phone: 0049-30-8445 2560
Fax: 0049-30-8445 4448

Gabriel Steiner, MD
Department of Urology
Rhön-Klinikum AG Meiningen
Bergstr. 3
D-98617 Meiningen

Phone: 0049-3693-900

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1. Introduction

1.1. Bladder Cancer

1.1.1. Incidence and epidemiology

Cancer of the urinary bladder is the fourth most common cancer in males and the fifth most common cause of cancer deaths in Europe. It accounts for 4% of all cancer deaths in men. The highest incidence rates are seen in Denmark, Belgium, Italy, and the United Kingdom. Risk factors in Europe include tobacco smoking and a variety of other occupational exposures [Jensen et al., 1990]. The estimated incidence of bladder cancer in the US for 1995 was more than 50,500 and the estimated number of deaths was more than 11,200 [American Cancer Society, Brochure, 1995]. Bladder cancer appears more frequently in the elderly (peak incidence in the seventh decade) and in males (3 males to 1 female) [DeVita et al., 1993; Scher and Norton, 1992]. Worldwide, the vast majority of bladder tumors are transitional cell carcinomas (TCC) but in countries where bilharzia infestation is endemic, mainly squamous cell carcinomas occur. The incidence of bladder cancer worldwide continues to rise by 5 to 10% every 5 years which may be attributed to the increase in tobacco use, especially in adolescents. Sixty to eighty per cent of all TCC are superficial lesions, the remaining portion of the tumors being invasive.

1.1.2. Therapy of locally advanced disease

The standard treatment for patients in the United States and Germany with muscle invasive bladder tumors with metastasis confined to the locoregional lymph nodes usually is radical cystectomy and bilateral pelvic lymph node dissection. Surgery alone cures approximately 15-20% of the patients. The remaining 80-85% will develop metastatic disease within 2 years after the initial operation and subsequently die of the disease.

1.1.2.1. Adjuvant Chemotherapy for locally advanced disease

In order to improve survival of this patient group, the administration of adjuvant chemotherapy seems to be promising. Three prospective trials comparing cystectomy alone with cystectomy plus adjuvant cisplatin based chemotherapy have been published. (Skinner et al., 1991; Stöckle et al., 1995 and 1996; Freiha et al., 1996). These trials are all criticized for methodological problems and small sample size, but uniformly demonstrate an improvement of progression free survival by platinum based adjuvant treatment. The value of platinum-based adjuvant chemotherapy for suitable patients...
is presently controversially discussed: Adjuvant treatment of younger patients with sufficient kidney function is common practice in the United States (the Eastern Cooperative Oncology Group presently compares M-VAC with Carboplatin and Paclitaxel as adjuvant approach [ECOG protocol 1857]) and Germany (the genito-urinary group of the German Cancer Society will finish recruitment of 320 patients for a trial comparing M-VEC versus Cisplatin and Methotrexat presumably in the summer of 2000 [AUO AB05/95]). In contrast, countries like the Netherlands still regard patients with lymph node involvement as incurable. In these countries, patients with lymph node metastases are not at all treated with curative intent and receive palliative treatment as soon as they develop symptomatic tumor progression. Preliminary and unpublished data from the ongoing German trial suggest a progression free long-term survival chance of about 35% in lymph node positive patients treated with radical cystectomy and platinum-based adjuvant chemotherapy. If these results will be confirmed by long-term observation of all patients at risk, the „Dutch attitude“ could no longer be regarded as standard of care.

Many cystectomy patients however, are regarded unsuitable for adjuvant platinum-based chemotherapy for various reasons such as age, compromised kidney function or postoperative morbidity. The mean age of cystectomy patients in Germany for instance is presently greater than 70 years and the before mentioned German protocol for adjuvant treatment excludes patients above the age of 70. Therefore, the majority of cystectomy patients for whom adjuvant treatment could be beneficial with regard to tumor stage are presently left without adjuvant treatment because of the presumed toxicity of M-VAC or comparable platinum-based regimens.

These problems can potentially be circumvented with the advent of less toxic chemotherapeutic agents like Gemcitabine, for which in the metastatic situation an activity against transitional cell carcinoma was found in phase-2-trials. In these studies the activity of Gemcitabine seems comparable to the activity of cisplatin as the most active substance of the M-VAC regimen. As Gemcitabine can also be administered in patients with impaired kidney function, it seems of special interest to evaluate whether adjuvant Gemcitabine monotherapy can improve survival in cystectomy patients treated for locally advanced transitional cell carcinoma who are regarded unsuitable for standard platinum based chemotherapy. In the current study early adjuvant treatment will therefore be compared with an expectant „watchful waiting“ supplemented by delayed, progression-triggered treatment strategy. The “wait and see” strategy represents the present standard of care for the patient group concerned.
1.1.3. Metastatic disease

Without treatment patients with metastatic urothelial tumors die of their disease. Before the development of effective chemotherapy, median survival rates rarely exceeded 3 to 6 months. Even with the most aggressive chemotherapy regimens, the overall median survival rarely exceeds 13 months and there is considerable treatment-related toxicity and morbidity although long-term survival is achieved in a few patients [Scher and Norton, 1992].

TCC is sensitive to several single agents with different mechanisms of action. The overall response to these single-agent regimens tends to last 3 to 4 months. Cisplatin is felt to be the most effective single agent, accounting for response rates of 34% in single-centre and 17% in randomized studies [Scher and Norton, 1992]. However, administration of cisplatin is limited: adequate dosage of cisplatin in patients with reduced renal function is not feasible, the necessary fluid load is often not manageable in patients with impaired cardiac function.

Methotrexate is another single-agent anticancer drug utilized in bladder cancer with an overall response rate of 29% [Yagoda, 1987]. Other agents with activity in TCC given as single medication include adriamycin, vinblastine, 5-fluorouracil, paclitaxel, gallium nitrate and Gemcitabine (see 1.3.2., Table 1) [Roth, 1995].

1.1.3.1. Gemcitabine - preclinical data

Gemcitabine (difluorodeoxycytidine), an analogue of cytosine arabinoside (ara-C), is a pyrimidine antimetabolite [Hertel et al., 1988]. The mechanism of action of Gemcitabine has been well characterised. Gemcitabine is deaminated intracellularly by deoxycytidine deaminase to difluorodeoxyuridine or activated by deoxycytidine kinase to difluorodeoxycytidine monophosphate (dFdCMP). Difluorodeoxyuridine is inactive, while dFdCMP is further metabolized to difluorodeoxycytidine diphosphate (dFdCDP) and difluorodeoxycitidine triphosphate (dFdCTP), which, when incorporated into DNA, results in chain termination. In comparison to ara-C incorporation into DNA, dFdCTP is less readily excised from DNA by DNA exonuclease. Thus, dFdCTP accumulates intracellularly to a greater degree than ara-C. This may in part account for its different spectrum of preclinical and clinical activity. In addition, Gemcitabine inhibits ribonucleotide reductase, an enzyme that produces deoxynucleotides that are required for DNA synthesis. Gemcitabine is active in a variety of murine solid tumors and leukemias, as well as several human tumor xenografts [Hertel et al., 1990].

After infusion of 1000 mg/m² Gemcitabine over 30 minutes maximal serum levels of 10 to 40 µg/ml are achieved. The extracellular half time is approximately 30 minutes. Gemcitabine is metabolized to...
an extent of 91-98% to the inactive metabolite 2’-deoxy-2’,2’-difluorouridine (dFdU) [Allerheiligen et al., 1992]. The deamination takes place by cytidin-deaminases in liver, kidneys and other tissues as well as in blood. After an infusion in the above mentioned dosage 92-98% of this dose are found in the urine after a period of 1 week. Elimination of the original substance and dFdU takes place to an extent of 99% via the urine, less than 1% is eliminated via the feces. Cytostatically active metabolites are not found either in plasma or urine. Plasma protein binding of Gemcitabine is less than 10%.

1.2. Gemcitabine - Phase 1 Data

1.2.1. Hematological toxicity

Initial phase 1 studies using a short infusion schedule with Gemcitabine given weekly for 3 weeks followed by 1 week of rest established 790 mg/m²/week as the maximum tolerated dose (MTD). Dose-limiting toxicity (DLT) was myelosuppression with thrombocytopenia being more significant than neutropenia [Abbruzzese et al., 1991a]. More recent phase 1 and 2 trials have established 1250 mg/m²/week as a well-tolerated dose in chemonaive patients [Fosella et al., 1993, Abbruzzese et al., 1991b; Casper et al., 1991]. Principal toxicities reported were hematologic, with World Health Organization (WHO) grade 4 neutropenia and thrombocytopenia occurring rarely, reversible elevation in hepatic transaminases, proteinuria, mild skin rash with and without pruritus and nausea and vomiting. A review of 201 patients treated with 1250 mg/m²/week who had not received prior chemotherapy revealed the following toxicity profile: neutropenia WHO grade 3 and 4 in 23% and 6%, respectively; reversible elevation in hepatic transaminases WHO grade 3 and 4 in 6% and 2%, respectively; WHO grade 3 proteinuria occurred in less than 1%; WHO grade 3 nausea and vomiting in 10%; and mild skin rash in 26% with pruritus occurring in 10% [American Cancer Society, 1995]. Other phase 1 studies have been conducted using other more frequent dosing regimens (i.e., twice weekly and daily times five). These studies reported significantly more non-hematologic toxicities such as flu-like symptoms and rash with the DLT being thrombocytopenia [DeVita et al., 1993; Scher and Norton, 1992]. The daily times five phase 1 trial was stopped because of sporadic fever and occasional severe hypotension [Yagoda, 1987].

1.2.2. Renal toxicity

No severe renal damage was observed under Gemcitabine monotherapy. Rarely, mild proteinuria (WHO grade II) occurred but the connection to Gemcitabine could not be proven. [Green, 1996].
Rarely, hemolytic uremic syndromes have been observed in patients receiving Gemcitabine with a crude overall incidence rate of 0.015% [Fung, 1999].

1.2.3. Pulmonary toxicity

Dyspnea of any grade occurred in 8.2% of patients treated with Gemcitabine (790 patients in 18 studies analyzed) [Green, 1996]. Grade III and grade IV dyspnea was observed in 1.6 and 0.2%, respectively.

1.2.4. "Flu-like symptoms"

Symptoms, such as headache, fever, chills, myalgia and fatigue were described in 19% of the patients. All these symptoms were mild and lead to termination of the therapy in only 0.1%. [Green, 1996]

1.2.5. Alopecia

The rates for alopecia were the following: grade I: 10%, grade II: 3% and grade III: <1%, respectively.

1.2.6. Peripheral edema

Edema occurred in 28.4% of the patients. They usually were mild and reversible after termination of the therapy. In less than 1% edema lead to premature ending of the study. No cardiac, renal or hepatic cause could be found in these cases [Green, 1996].

1.2.7. Neurotoxicity

Neurotoxicity is seldomly described. Asthenia, mild paresthesia and constipation were described [Green, 1996].

1.3. Gemcitabine - Phase 2 Data

1.3.1. Overview

Gemcitabine has now undergone considerable testing in various malignancies, and has exhibited activity in non-small cell lung cancer (NSCLC), pancreatic cancer, bladder cancer, advanced breast carcinoma, cisplatin-refractory ovarian carcinoma and squamous cell carcinoma of the head and
neck as a single agent. The majority of ovarian cancer patients had undergone prior treatment with cisplatin-based chemotherapy [Lund et al., 1993].

1.3.2. Single Agent Activity in Bladder Cancer

Gemcitabine appears to have significant single agent activity in bladder cancer since it has been studied as a single agent in one phase 1 and six phase 2 studies in advanced or metastatic bladder cancer. Gemcitabine seems to be the only substance inducing response rates similar to Cisplatin as a single agent. Details of these studies are given in Tables 1 and 2. Responses have been seen in the liver, lung and bone as well as in lymph node metastases.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Phase</th>
<th>Gemcitabine (mg/m²)</th>
<th>Patient Population</th>
<th>No. Pts.</th>
<th>*CR (n)</th>
<th>**PR (n)</th>
<th>***RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollera, 1994</td>
<td>I</td>
<td>875 – 1370 x 3</td>
<td>Prior MVAC</td>
<td>15</td>
<td>1</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>Stadler, 1997</td>
<td>II</td>
<td>1200 x 3</td>
<td>Adjuvant &gt;6 mths previously</td>
<td>44</td>
<td>4</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Moore, 1997</td>
<td>II</td>
<td>1200 x 3</td>
<td></td>
<td>37</td>
<td>3</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Lorusso, 1998</td>
<td>II</td>
<td>1200 x 3</td>
<td></td>
<td>31</td>
<td>4</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Gebbia, 1998</td>
<td>II</td>
<td>1000 x 3</td>
<td></td>
<td>24</td>
<td>1</td>
<td>6</td>
<td>29</td>
</tr>
</tbody>
</table>

*CR: complete response, **PR: partial response, ***RR: rate of response (see 3.9.1.5. Efficacy criteria)

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Dose Gemcitabine (mg/m²)</th>
<th>WBC</th>
<th>Neutrophils</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollera, 1994</td>
<td>875-1370 x 3</td>
<td>53% (2-3)</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Stadler, 1997</td>
<td>1200 x 3</td>
<td>3%</td>
<td>0%</td>
<td>18%</td>
</tr>
<tr>
<td>Moore, 1997</td>
<td>1200</td>
<td>3%</td>
<td>0%</td>
<td>13%</td>
</tr>
<tr>
<td>Lorusso, 1998</td>
<td>1200 x 3</td>
<td>9%</td>
<td>3%</td>
<td>13%</td>
</tr>
<tr>
<td>Gebbia, 1998</td>
<td>100 x 3</td>
<td>12.5%</td>
<td>0%</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

n.d.: not determined
These data demonstrate that Gemcitabine is a promising agent for metastatic transitional cell bladder cancer, including patients previously exposed to MVAC chemotherapy. In addition, the toxicity profile was modest and similar to that seen in patients with other tumor types, i.e., NSCLC.

Patients with impaired renal function and who are older than 70 years are excluded from participation in many ongoing chemotherapy studies for TCC. However, since bladder cancer appears in the elderly patient with a peak incidence in the 7th decade [DeVita, 1993; Scher and Norton, 1992] and these patients suffer from reduced renal function, caused either by the tumor or other disease (i.e. diabetes, hypertension), they could not be treated by chemotherapy to date.

1.3.3. Single Agent Activity in Other Tumors

Gemcitabine showed modest single-agent activity given 1000 mg/m² x3 in advanced and metastatic breast carcinoma, demonstrating an overall response rate of 14.3% with a median survival of 15.2 months [Possinger et al., 1999]. Other reports confirm relatively high response rates in bladder (31%), breast (33%), ovarian (22%), pancreatic (11%), non small cell lung cancer (22%) and small cell lung cancer (27%) [van Moorsel et al., 1997]. Gemcitabine treatment was also able to improve clinical symptoms, while toxicity was not severe with mild myelosuppression. These encouraging data are the rationale to introduce Gemcitabine in an adjuvant setting for the treatment of locally advanced bladder cancer in elderly patients and patients with reduced renal function.
2. Objectives

2.1. Primary Objective

The primary objective of this study is to analyse time to tumor progression in patients cystectomized for locally advanced TCC of the bladder, who are not suitable for a cisplatin-based chemotherapy (i.e. postoperative reduced renal function, advanced age).

Patients are randomized to receive either adjuvant Gemcitabine immediately after radical operation (treatment arm A) or no treatment (control arm B). Patients in control arm are to be treated with Gemcitabine as soon as tumor progression becomes evident clinically and/or radiologically.

2.2. Secondary Objectives

The secondary objectives of this study are:

- estimation of time-specific survival probabilities irrespective of causes of death
- assessment of toxicity and tolerability of Gemcitabine
- description of survival experience of patients in the control arm beyond the time of initiating chemotherapy
- assessment of quality of life (EORTC QLQ-C30, Attachment 7).
3. Study design

3.1. Summary

This is an open-label, prospective, multicenter, randomized, controlled phase 3 two-arm study using Gemcitabine as single agent in chemonaive cystectomy patients with locally advanced TCC of the bladder in an adjuvant setting. The patients will receive the following treatment:

Arm A (treatment): Gemcitabine 1250 mg/m² intravenously once a week for 2 weeks (days 1 and 8) followed by 1-week rest period. Repeat cycle on day 22. Maximum of 6 cycles. It is recommended to begin treatment within 6 weeks after radical cystectomy; although, initiation of adjuvant Gemcitabine until 3 months after radical operation is tolerable.

Arm B (control): No immediate post-surgery treatment. Watchful waiting; treatment only conditionally in case of progression with Gemcitabine (dose and schedule as in arm A).

3.2. Investigator Information

The name, title, and institution of the investigators are available from the principal investigator. If an investigator changes institutional affiliation after the study has been approved by an ethical review board or a regulatory agency, this addition will not be considered a change to the protocol, but the contacts for this protocol will be updated to provide this information.

3.3. Final Report Signature

The final report coordinating investigator will sign the final clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.
3.4. Study Population

3.4.1. Entry Procedures

A written informed consent will be obtained from each patient after the nature of the study is explained.

3.4.2. Criteria for Enrollment

Enter  The act of obtaining informed consent for participation in a clinical study from individuals deemed potentially eligible to participate in the clinical study. Individuals entered into a study are those for whom informed consent documents for the study have been signed by the potential study participants or their legal representatives. Adverse events are reported for each individual who has entered the study, even if the individual is never assigned either to the treatment or the non-treatment (control) group (enrolled).

Enroll  The act of assigning an individual to a group. Individuals who are enrolled in the study are those who have been assigned to either the treatment or the non-treatment (control) group.

A person who has been entered into the study is potentially eligible to be enrolled in the study, but must meet all criteria for enrollment specified in the protocol before being enrolled (assigned either to the treatment or the non-treatment group). Individuals who are entered into the study but fail to meet the criteria for enrollment are not eligible to participate in the study and will not be enrolled.

Adverse events are reported for all individuals who have entered the study and all individuals who are enrolled in the study (assigned to treatment groups).

3.4.2.1. Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria. In addition there will be a second check of eligibility criteria just prior to randomization by the Coordinating Data Center.

1. Status after radical cystectomy for transitional cell carcinoma of the bladder, stages pT3a, pT3b, pT4a and/or pN1, pN2 (but no more than 5 lymph nodes positive for tumor) [see Attachment 2 - UICC criteria, 1997]. Transitional cell carcinoma may be with or without
squamous cell carcinoma and/or adenocarcinoma components. Complete tumor removal by radical operation has to be established macroscopically and microscopically (R0 resection).

**Comment:**

*Patients with more than 5 lymph nodes positive for tumor have a significantly worse outcome independent of adjuvant chemotherapy and should therefore be excluded from the study [Stöckle et al., 1996].*

**Surgical Considerations:**

Radical cystectomy denotes the removal of the entire bladder, prostate and seminal vesicles in men, and removal of all anterior pelvic organs in the female, including if indicated, a portion of the anterior vagina (anterior exenteration). The method of urinary diversion is left to the discretion of the investigator, including ileal conduit, various forms of pouches and neobladder constructions.

*Bilateral pelvic lymphnode dissection is a prerequisite for correct staging and should include a full dissection of the lymph nodes bordered by the internal iliac arteries, external iliac arteries, and the pelvic floor bilaterally (including obturator nodes) Obturator and iliac lymph nodes should be separately investigated by the pathologist. The pathologist has to be made aware that assessment of every single extirpated lymph node is required for correct staging. TNM-classification by the latest edition is to be applied [UICC, 1997].*

2. Patients regarded inappropriate for cisplatin based chemotherapy (i.e. impaired renal function with at least 30 ml/min calculated creatinine clearance and serum-creatinine less than 3.0 mg/dl, age ≥70) are eligible for study enrollment [calculation of creatinine clearance according to Cockcroft and Gault formula - Attachment 6]. Decision left to the investigators descretion.

3. Patient has no prior history of systemic chemotherapy regimens. Previous local intravesical adjuvant chemotherapy or immunotherapy is allowed.

4. Prior radiation therapy is allowed if it has been completed at least 12 weeks before enrollment into the study and the patient has recovered from all toxic effects.

5. Performance status of 60 or higher on the Karnofsky Scale (Attachment 1).

6. Patient compliance, mental state, and geographic proximity allow adequate followup.

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7. Adequate bone marrow reserve: white blood cell (WBC) count $\geq 3.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin $\geq 10$ g/dL (or $\geq 6.2$ mmol/L or $\geq 100$ g/L).

8. Adequate liver function with bilirubin $\leq 1.25$ times above upper limit of normal range; alanine transaminase (ALT) or aspartate transaminase (AST) $\leq 2.5$ times normal upper limit.

9. Males or females at least 18 years of age who are considered fit for Gemcitabine chemotherapy.

10. Signed informed consent by the patient.

3.4.2.2. Exclusion Criteria

Patients will be excluded from the study for any of the following reasons:

1. Tumor was not completely removed (visible tumor or enlarged lymph nodes left or positive margins microscopically - R1 or R2 resection)

2. Patient has a distant metastasis or metastases.

3. Tumor stage pT4b or more than 5 locoregional lymph nodes are positive for tumor.

4. Adeno- and/or squamous cell carcinoma of the bladder without transitional cell carcinoma component (different responses to chemotherapy).

5. Time interval between radical cystectomy and the first day of chemotherapy exceeds 3 months for patients enrolled in the treatment arm.

6. Serum-creatinine $\geq 3.0$ mg/dl ($\geq 265$ mmol/l)

7. Active infection (at the discretion of the investigator).

8. Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator).

9. Patients with a history of prior malignancy other than basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or incidental carcinoma of the prostate must be clinically free of disease for at least 5 years prior to study entry

10. Use of any investigational agent in the month before enrollment into the study.

11. White blood cell (WBC) count $< 3.5 \times 10^9$/L or platelets $< 100 \times 10^9$/L or hemoglobin $< 10$ g/dL (or $< 6.2$ mmol/L or $< 100$ g/L).

12. Bilirubin $\geq 1.25$ times above upper limit of normal range; alanine transaminase (ALT) or aspartate transaminase (AST) $\geq 2.5$ times upper limit of normal range.
3.4.2.3. Violation of Criteria for Enrollment

The criteria for enrollment must be followed explicitly. If there is inadvertent enrollment of individuals who do not meet enrollment criteria, these individuals should be discontinued from the study. Such individuals can remain in the study only if there are ethical reasons to have them continue. In these cases, the investigator must obtain approval from the principal investigator for the study participant to continue in the study.

3.4.3. Sample Size

Sample size calculation shows that n=89 evaluable patients are required in each arm of the trial in order to attain a power of 80% in a log-rank test (one-sided) at the 5% level against the alternative that the probability of remaining progression-free for at least 36 months is 15% larger in the treatment as compared to the control arm. This number has been computed under the following additional assumptions:

(i) Patient recruitment will be done uniformly over a period of 36 months.
(ii) Minimal followup time will be 24 months for event-free patients.
(iii) Except for possible censoring on the right, the distribution of the survival times are exponential.
(iv) In the control arm, the true probability of remaining progression-free for the first 3 years is 20%.

3.5. Patient Assignment and Randomization

This is a competitive enrollment multicenter study. Patients will be randomized either to arm A (therapy with Gemcitabine) or to arm B (control group without immediate therapy, but with the option of receiving therapy in case of a progression). The recruitment process will be continued until for both arms the number of evaluable patients (enrolled patients except for drop-outs) equals the sample size required according to §3.4.4. In order to accommodate possible asymmetry in drop-out rates between both arms of the study (in the control arm, the proportion of patients terminating follow-up before a progression is expected to be distinctly lower than in arm A due to refusal of complying with the medication regime) an adaptive two-stage randomisation scheme will be applied. At a first stage, common 1:1 randomisation by means of blocks of length four containing 2 A’s and 2 B’s will be used. After completion of about 30 blocks of this type, the rate of patients refusing to really undergo the chemotherapy regime will be estimated from the data accumulated up to that time.
For the second half of the randomisation process, blocks of a suitably modified composition will be used (e.g. 30 blocks containing 2 A’s and a single B, if in the first half, the proportion of noncompliant patients was observed to be about 30%). Of course, if the noncompliance rate turns out negligible, the structure of the permuted blocks will be kept the same.

In order to reduce the potential imbalancing effects of non-completion of blocks as much as possible in practice, only centers guaranteeing a minimum number of 4 patients to be recruited will be admitted to participate in the trial. Patients recruited by centers which do not meet this requirement will be excluded from final data analysis.

The randomisation code and sets of sealed envelopes will be generated by the statistician in charge of the biometric guidance of the trial by means of special computer program. Details will be presented at a central start-up meeting.

3.6. Dosage and Administration

3.6.1. Application of Study Drug

Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1000 mg of Gemcitabine as the hydrochloride salt, mannitol, and sodium acetate. The lyophilized product should be stored below 30°C. Drug will be reconstituted with normal saline added to the vial to make a solution containing 10 mg/mL ideally. The concentration for 200 mg and 1000 mg vials should be no greater than 40 mg/mL. An appropriate amount of drug will be prepared with normal saline and administered as a continuous infusion over approximately 30 to 60 minutes, with 30 minutes being ideal. Once the drug has been reconstituted it should be stored at room temperature and used within 24 hours.

3.6.2. Dosage

3.6.2.1. Dosage Selection and Administration Procedures

Study drug should be given as stipulated, but may be given within a window of 2 days if circumstances dictate this (i.e. holidays etc.) Gemcitabine will be given on days 1 and 8 of each 21 day cycle. A cycle is defined as 2 consecutive weeks of treatment followed by 1 week of rest. A dose of 1250 mg/m² of Gemcitabine will be administered intravenously for 30 - 60 minutes on the day of therapy, with 30 minutes being ideal.
Calculate the body surface area of the patient according to actual height and weight at the beginning of each cycle.

### 3.6.2.2. Dosage Adjustments

#### 3.6.2.2.1. Dose Escalation

There will be no dose escalation of Gemcitabine in this study.

#### 3.6.2.2.2. Dose Adjustment of Gemcitabine

Dose adjustments within a cycle of the dose of Gemcitabine as appropriate in the schedule will be made following the guidelines shown in Table 5 based on weekly white blood cell (WBC) and platelet counts, and clinical assessment of non-hematologic toxicities.

No new cycle of Gemcitabine should start unless the absolute leucocyte count is ≥3.5 x10⁹/L and the platelet count is ≥100 x10⁹/L taken within 24 hours prior to therapy.

Doses held due to toxicity or missed will not be given at a later time. If the dose held or missed was to be given on day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient (i.e., 1-2-R, X-1-2-R, etc). If the second (day 8) dose is held or missed, the cycle would continue per protocol with one dose not given (ie, 1-2-R, 1-X-R, etc). The following week a dose would be administered (if toxicity permits) and considered the beginning (day 1) of a new cycle.

A patient who cannot be administered drug for 4 weeks from the time of the last study drug administration must be discontinued from the study unless approved by the principal investigator.

#### 3.6.2.2.3. Dose Adjustments for Hematologic Toxicities

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day 8 Total WBC (x10⁹/L)</th>
<th>Platelets (with no evidence of bleeding, ie, petechiae) (x10⁹/L)</th>
<th>per cent of full dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>≥3.5</td>
<td>and</td>
<td>≥100</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1.9 – 3.49</td>
<td>or</td>
<td>75-100</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>&lt; 1.9</td>
<td>or</td>
<td>&lt; 75</td>
</tr>
</tbody>
</table>

If there is any evidence of bleeding complications, the dose should be omitted.

The myelosuppression seen with Gemcitabine tends to be short lived and non-cumulative and so no
account of nadir values will be taken for subsequent cycles. All doses will be administered according to the WBC and platelet count in the 24 hour period prior to dosing of Gemcitabine.

### 3.6.2.2.4. Dose Adjustments for Non-hematologic Toxicities

#### Table 6  Dose Adjustments for Renal Toxicity

<table>
<thead>
<tr>
<th>Serum Creatinine</th>
<th>Gemcitabine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.0 mg/dl; &lt; 265 mmol/l</td>
<td>100%</td>
</tr>
<tr>
<td>≥3.0 mg/dl; ≥265 mmol/l</td>
<td>Omit</td>
</tr>
</tbody>
</table>

#### Table 7  Dose Adjustments for Other Non-hematologic Toxicities

(Pain, pulmonal, diarrhea, cutaneous, allergic, fever, cardiac, infection except nausea, vomiting and alopecia)

<table>
<thead>
<tr>
<th>WHO Grade</th>
<th>Gemcitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>50% or omit&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>50% or stop&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> This decision will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the physician-investigator.

<sup>b</sup> Patients will be removed from study unless they are responding as patients in ArmB developing progressive disease.

In case of minor pulmonal, cutaneous, allergic or fever toxicities use of three times dexamethasone 8mg (just before scheduled Gemcitabine infusion, as well as 12 and 24 hours after infusion) should be considered.

### 3.7. Blinding

This is an open-label, randomized and controlled study, so the identity of the treatment will be known to the investigator and the patient. As is so often the case in oncological trials, there are obvious reasons forbidding even single blinding of the study.
3.8. Concomitant Therapy

No other chemotherapy, immunotherapy, anticancer hormonal therapy or experimental medications will be permitted while the patient is on the study. Any disease progression requiring other forms of specific antitumor therapy will be a cause for early discontinuation in this study.

Palliative radiotherapy after progression and following termination of the study for bone metastases should not be administered in the first 48 hours following Gemcitabine administration, because of the potential for radiosensitization.

Patients should receive full supportive care. Prophylactic use of growth factors is not recommended, but if administered, this should be recorded on the case report form.

Drugs with potential for nephrotoxicity should be avoided if at all possible.

Steroids will be allowed for prophylaxis of nausea and vomiting.

3.9. Efficacy and Safety Evaluations

See Schedule of Events (Attachment 3).

3.9.1. Efficacy

3.9.1.1. Baseline assessment

No more than 1 week before enrolling into the study, the disease status of each patient will be assessed with the following procedures:

- Medical history and physical examination, including measurements of height and weight.
- Evaluation of performance status (Karnofsky scale).
- Evaluation of quality of life (QLQ-30 EORTC)

3.9.1.2. Followup schedule

For evaluation schedule (until relapse or progressive disease develops) see Attachment 3b.

3.9.1.3. Variables to be monitored for purposes of efficacy assessment

At each visit, evaluation is based on the following investigations and findings:

- Plain chest radiograph with consecutive CT of the thorax if suspicious lesions need to be clarified.
- Weight measurement.
- Performance status evaluation.
- Limited medical history and physical examination.
- CT or MRI of the abdomen should be performed 6, 12 and 20 months after cystectomy, or as soon as clinical signs of intra-abdominal tumor progression become evident.
- Patients will be questioned and examined for disease progression, and any clinical signs and symptoms will be followed by appropriate tests (i.e. bone scan, CT/MRI) to demonstrate a possible progressive disease.

3.9.1.4. Additional monitoring during medication

Before every therapy cycle and 4 weeks after the last dose of study drug, in addition to the investigations listed in 3.9.1.2, the following diagnostic tools will be applied (Attachment 3a):

- Hematology, chemistry
- WHO toxicity grading.

3.9.1.5. Ascertainment of progression

A panel of independent experts might evaluate the diagnosis of progression by applying standard oncologic criteria. About 90% of cases with progressive disease will presumably occur systemically, whereas 10% will be located retroperitoneally or locally. Symptoms such as skeletal pain, unintended weight loss, ileus, progressive lymphedema of lower extremities etc. should be evaluated by appropriate diagnostic measures such as CT, MRI, bone scan etc. Therefore, investigators should make available copies of all radiologic imaging studies for responding patients. The measurability of a tumor is defined as follows:

- Bidimensionally measurable - all tumor measurements will be recorded in centimeters using a ruler or calipers and consist of the diameter of the widest portions of the tumor and the greatest diameter perpendicular to that line. Ideally measurable lesions on CT scans or MRI scans will have their dimensions indicated with calipers and the measurements calculated by the computer.

- Unidimensionally measurable (evaluable):
- Liver enlargement due to tumor involvement - sum the distances of the inferior liver edge from the xiphoid notch and the right and left costal margins in the respective mid-clavicular lines.
- Other lesions where only one dimension is measurable - record that single dimension.
- Nonmeasurable - the following manifestations are not considered measurable:
  - lymphangitic pulmonary metastases.
  - ascites.
  - pleural effusions.
  - blastic or mixed bony metastases.
  - abdominal masses which can be palpated but not measured.

The same assessment method used to determine the disease status at baseline will be used consistently for efficacy evaluation throughout the study. Included in the evaluations are the following modified WHO criteria:

- **Complete response** (CR): The disappearance of all known disease, determined by two observations not less than 3 weeks apart.
- **Partial response** (PR): At least a 50% decrease in total tumor size of the lesions that have been measured to determine the effect of therapy by two observations not less than 3 weeks apart. In addition, there may be no appearance of new lesions or progression of any lesion.
- **Stable disease** (SD): A 50% decrease in total tumor size cannot be established, nor is a 25% increase in the size of one or more measurable lesions demonstrated.
- **Progressive disease** (PD): At least a 25% increase in the size of at least one measurable lesion or the appearance of new lesions.

The duration of a PR is measured from the time of the initial administration of the first dose of chemotherapy until the time of documented progressive disease. The duration of CR is measured from the time the CR was documented until the date of the first observation of disease progression. Time to progression and to death from the tumor under investigation is measured from the date of cystectomy. In patients randomised to arm B receiving delayed chemotherapy, residual life time is measured from the date of diagnosis of PD.
3.9.2. Safety

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the principal investigator to any serious event.

3.9.2.1. Clinical Adverse Events

An adverse event is any undesirable experience possibly related to the use of a drug.

At the first visit, study site personnel will question each patient and will note the occurrence and nature of presenting condition(s) and any preexisting condition(s). At subsequent visits, site personnel will again question the patient and will note any change in the present condition(s), any change in the preexisting condition(s), and/or the occurrence and nature of any adverse events.

For purposes of collecting and evaluating all information about the drugs used in clinical trials, an adverse event is defined as any undesirable experience that occurs after informed consent has been obtained, without regard to treatment group assignment, even if no study medication has been taken. Lack of drug effect is not an adverse event in clinical trials, because the purpose of the clinical trial is to establish drug effect.

3.9.2.1.1. Adverse Event Reporting Requirements

Reporting Serious Adverse Events

Common toxicities observed for chemotherapy, and progressive disease and events secondary to progressive disease are generally excluded from reporting. However, in cases where the specificity or severity of an event is not consistent with the risk information, the event should be reported.

Study site personnel must report to the principal investigator or manufacturer of the drug (Lilly Deutschland GmbH) immediately, by telephone (see title page), any serious adverse event (see section 3.9.2.1.2. below). For recommendations for reporting serious adverse events, see Attachment 4.

Even if a telephone report has been made for a serious adverse event, study site personnel must also promptly report these events to the principal investigator on the clinical report form, as for all adverse events.

If a patient's dosage is reduced or if a patient is discontinued from the study because of any significant laboratory abnormality, inadequate response to treatment, or any other reason, study site
personnel must report and clearly document the circumstances and data leading to any such dosage reduction on the clinical report form.

3.9.2.1.2. **Serious Adverse Events**

Study site personnel must report to the principal investigator or the manufacturer of the drug (Lilly Deutschland GmbH) immediately, by telephone, any adverse event from this study that is alarming or that:

- results in death (death due to tumor progression must NOT be reported)
- results in initial or prolonged inpatient hospitalisation
- is life-threatening
- results in severe or permanent disability
- results in cancer (other than cancers diagnosed prior to enrollment in studies involving patients with cancer)
- results in a congenital anomaly

All serious adverse events should be reported within 24 hours of the event to the principal investigator or the manufacturer of the drug (Lilly Deutschland GmbH).

Note: planned hospitalizations (e.g., for surgical procedures) are not entered as SAEs. Hospitalisation for study drug administration is not a serious adverse event.

Common toxicities observed for chemotherapy, and progressive disease and events secondary to progressive disease are generally excluded from reporting. However, in cases where the specificity or severity of an event is not consistent with the risk information, the event should be reported.

Patients should be closely followed for adverse events while receiving study drug and for 30 days after the last dose of study drug in order to detect delayed toxicity. After this period, investigators should only report serious adverse events which are felt to be causally related to study drug therapy.

3.9.2.2. **Clinical Laboratory Tests**

No more than 2 weeks before enrolling into the study, the disease status of each patient will be assessed with the following tests:
- Full blood count (FBC) (hemoglobin, white blood cells [WBC], neutrophils, platelets), prothrombin and INR (international normalized ratio).
- Blood chemistries: bilirubin, alkaline phosphatase, ALT and AST, BUN, creatinine, calcium, total protein, albumin, sodium and potassium, and lactic dehydrogenase (LDH).
- Calculated urinary creatinine clearance (Cockcroft and Gault Formula, Attachment 6).
- Electrocardiogram (ECG).
- Vital signs (blood pressure and pulse rate).

During therapy, the patients will be assessed as follows (Attachment 3a):
- Full blood count (FBC)
- Serum-creatinine
- Toxicity rating using the WHO scale at the end of each cycle (Attachment 5).
- Number of in-patient hospitalisations and length of stay.
- Otherwise a generally established standard of care for oncologic patients is to be applied.

Post-therapy (4 weeks after the last dose of study drug):
- Same safety assessments (excluding vital signs, PT and calculated creatinine clearance) as were performed at baseline.
- Toxicity rating using the WHO scale.
- Adverse events.

The local laboratory of the hospital performing the study will be used for all blood tests. Laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented on by the investigator by marking each value CS (clinically significant) or NCS (not clinically significant). Any clinically significant laboratory value that is outside a clinically acceptable range or that differs importantly from a previous value should be further explained on the clinical report form comments page.

When multiple laboratory values are out of range but not clinically significant, "all labs NCS" may be written on the laboratory page in place of marking each individual "NCS" laboratory value.
However, all clinically significant laboratory values must be individually marked and explained on the comments page.

3.9.3. Safety Monitoring

The principal investigator will be responsible for monitoring safety data throughout the course of the study.

3.9.4. Appropriateness and Consistency of Measurements

All efficacy and safety assessments used in these studies are standard for an oncology study.

3.10. Patient Disposition Criteria

3.10.1. Discontinuations

A patient will be discontinued from study drug therapy under the following circumstances.

- If there is evidence of progressive disease under therapy (arm A). Patients who develop a pleural effusion or ascites containing malignant cells will be considered as having progressive disease.
- If the attending physician thinks a change of therapy would be in the best interest of the patient.
- If the patient requests discontinuation.
- If the drug exhibits unacceptable toxicity.
- If the patient's best response has been achieved and/or a maximum of six cycles of therapy have been administered.

All patients will be followed in the study until their death.

3.10.2. Qualifications for Analysis

All patients will be evaluated for safety and for the primary efficacy analysis of progression-free and disease-specific survival as well as additional time-to-event variables of secondary interest. All patients randomised to arm B meeting the following criteria will be qualified for secondary tumor response analysis:

- Diagnosis of local relapse or metastatic TCC.
- No prior systemic chemotherapy.
- No concurrent systemic chemotherapy.
- Received at least 1 cycle of treatment (reductions and omissions accepted) and had at least one tumor assessment follow up.

In addition any patient withdrawn for toxicity reasons who has received less than one cycle will be qualified for safety.

3.10.3. Study Extensions

No extensions are planned in the study.

3.10.4. Post Study Followup

With all patients receiving drug treatment, visits will be arranged 4 weeks after the last dose (Attachment 3a) and subsequently according to the followup schedule 3.9.1.2. (Attachment 3b) in order to ascertain the time to possible tumor progression and death from specific tumor, respectively (for details see 3.9.1.2 and 3.9.1.3). All patients will be followed until death or until the closing date of the study. If alternative anti-cancer therapy is given, details of this will be collected.

3.11. Compliance

Study drug will be intravenously administered only at the investigational sites. As a result, patient compliance monitoring is ensured. Patients who return for followup visits will receive study drug unless they are encountering toxicity problems or their disease has progressed.

3.12. Quality Assurance

To ensure accurate, complete, and reliable data, the principal investigator and/or the Coordinating Data Center will:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction in all sections of the protocol, the completion of the clinical report forms, and study procedures (according to GCP rules).
- Perform periodic audits at the participating centers.
- Be available at all times for consultation and be in contact with the study-site personnel by mail, e-mail, telephone and/or fax.
· Review and check upon clinical report data using standard computer-aided procedures for detecting errors, missing entries and implausible values.

To ensure accurate, complete, and reliable data, the investigator will do the following:

· Keep records of laboratory tests, clinical notes, and patient's medical records in the patient's files as original source documents for the study for 15 years after completion of the study.

The monitors will check the patient data recorded against source documents at the study site.
4. Data Analysis Methods

4.1. General Conventions

All inferential procedures carried out for purposes of confirmatory statistical analysis of the data obtained on primary endpoints refer to error probabilities (significance levels and non-coverage risks in hypotheses testing and confidence interval estimation, respectively) of 5 percent. For additional exploratory analyses, p-values will be reported as descriptive measures rather than input into rigorous statistical decision procedures.

Interpretation and assessment of study results will be the responsibility of the principal investigator and the statistician cooperating with him in the group steering the trial. All computational steps to be taken in terms of the statistical analysis will be carried out by means of SAS (Statistical Analysis System, Release 6.12, 1996).

4.2. Data to be Analysed

The efficacy and safety analyses will be performed on data from qualified patients as defined in Section 3.10.2.

4.3. Patient Disposition

A detailed description of patient disposition will be provided. It will include:

- A decision on patient qualification.
- A summary of data on patient discontinuation.
- A summary of data on overall qualification status of all patients.
- An account of all identified protocol violations.

All patients entered in the study will be accounted for. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

4.4. Patient Characteristics

Patient characteristics covered by the case record forms will include a summary of the following:

- Patient demographics.
- Baseline disease characteristics.
- Pre-existing conditions.
- Prior therapies and response to therapy.
4.5. Efficacy Analysis

In all patients who meet the criteria for being evaluated for purposes of assessing treatment efficacy, time to tumor progression and death by the tumor of interest will be determined. Patients remaining free of progression or dying, if at all, from other causes by the end of the trial, will provide a censored value of the time until the respective event.

Primary analysis

For the time until reaching the primary endpoint (viz tumor progression), survival curves will be constructed by means of the well-known product-limit estimation technique of Kaplan and Meier (Kaplan and Meier, 1958). The survival curve obtained in the treatment arm (A) will be tested for superiority to that obtained in the control group (B) by means of the log-rank statistic (Kalbfleisch and Prentice, 1980).

Secondary analyses

The rate of patients from arm B responding to gemcitabine administered upon tumor progression and the corresponding confidence interval will be computed by means of standard techniques for binomial proportions. In addition, time-specific probabilities of surviving a progression under delayed gemcitabine medication will be estimated by means of the Kaplan-Meier method again. As far as being well defined, the median and the 1st and 3rd quartile of this distribution will be reported. Furthermore, changes in quality-of-life scores from baseline to some time during therapy and termination of adjuvant chemotherapy will be investigated.

For the primary endpoint (i.e. tumor-progression), comparison of the survivor curves by means of the log-rank test will be supplemented by analyses based on more complex regression models incorporating various potential influence factors like patient’s age at cystectomy, size of the center where he entered the study, etc.

4.6. Safety Analyses

All patients who are randomized will be evaluated for safety. Safety analyses will include the following:

- Concomitant drugs.

Other patient characteristics will be summarised as deemed appropriate.
- Summaries of the numbers of cycles of therapy administered and the number of dose reductions or omissions required in the study.
- Summaries of the adverse event rates and laboratory changes.
- Summaries of the number of WHO toxicity grades for laboratory and non-laboratory parameters.
- Summary of hospitalisations.
- Summary of the number of episodes of febrile neutropenia defined as a fever >38.0°C at a time when the WBC is <0.5 x 10⁹ /L.
- Details of any deaths due to study drug toxicity.

4.7. Interim Analyses

There is no interim analysis planned.
5. Informed Consent, Ethical Review, Regulatory Considerations

5.1. Informed Consent

The informed consent document will be used to explain in simple terms, before the patient is entered into the study, the risks and benefits to the patient. The informed consent document must contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time.

The investigator is responsible for obtaining informed consent from each patient or legal representative and for obtaining the appropriate signatures on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

5.2. Ethical Review

The investigator will provide the principal investigator with documentation of ethical review board approval of the protocol and the informed consent document before the study may begin at the site or sites concerned. The ethical review board(s) will review the protocol as required.

5.3. Regulatory Considerations

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represents the greater protection of the individual.

After reading the protocol, each investigator will sign two protocol signature pages and return one of the signed pages to the principal investigator (Attachment 8).
6. References


23. Roth BJ. Palliative Chemotherapy in Advanced Bladder Cancer. Seminars in Oncology 1995; 22 (supl.): 10-15


33. Yagoda A. Chemotherapy of Urothelial Tract Tumors. Cancer. 1987; 60: 574-585
## Attachment 1: Karnofsky Performance Status

<table>
<thead>
<tr>
<th>Activity Status</th>
<th>Point</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Activity</td>
<td>100</td>
<td>Normal, with no complaints or evidence of disease</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>Able to carry on normal activity but with minor signs or symptoms of disease present</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>Normal activity but requiring effort; signs and symptoms of disease more prominent</td>
</tr>
<tr>
<td>Self-Care</td>
<td>70</td>
<td>Able to care for self, but unable to work or carry on other normal activities</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>Able to care for most needs but requires occasional assistance</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Considerable assistance required, along with frequent medical care; some self-care still possible</td>
</tr>
<tr>
<td>Incapacitated</td>
<td>40</td>
<td>Disabled and requiring special care and assistance</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>Severely disabled; hospitalisation required but death from disease not imminent</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Extremely ill, supportive treatment, hospitalised care required</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Imminent death</td>
</tr>
<tr>
<td></td>
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</table>
Attachment 2: UICC Criteria for Bladder Cancer (5th Edition)

Stage Grouping

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
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<tbody>
<tr>
<td>Stage 0</td>
<td>Ta</td>
<td>N0</td>
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<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>
|                | T4b | N0  | M0  | (Excluded from this study)

TNM Criteria

Primary Tumor (T):
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Ta Noninvasive papillary carcinoma
Tis Carcinoma in situ: "flat tumor"
T1 Tumor invades subepithelial connective tissue
T2 Tumor invades muscle
  T2a Tumor invades superficial muscle (inner half)
  T2b Tumor invades deep muscle (outer half)
T3 Tumor invades perivesical tissue
  T3a Microscopially
  T3b Macroscopically (extravesical mass)
T4 Tumor invades any of the following:
  prostate, uterus, vagina, pelvic wall, abdominal wall
  T4a Tumor invades the prostate or uterus or vagina
  T4b Tumor invades the pelvic wall and/or abdominal wall

Regional Lymph Nodes (N):
Regional lymph nodes are those within the true pelvis; all others are distant nodes.
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node 2 cm or less in greatest dimension
N2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3 Metastasis in a lymph node more than 5 cm in greatest dimension

Distant Metastasis (M):
MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Approved by Lilly: 16 February 2000
### Attachment 3a: Therapy Schedule

**Arm A (immediate therapy) or Arm B (in case of progression)**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>4 wks after last dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td>15</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 wks</td>
<td>after</td>
<td>last</td>
<td>dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent signed</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Physical exam</td>
</tr>
<tr>
<td>Weight</td>
</tr>
<tr>
<td>Height</td>
</tr>
<tr>
<td>Karnofsky perform. stat.</td>
</tr>
<tr>
<td>Vital signs</td>
</tr>
<tr>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Serum Creatinine</td>
</tr>
<tr>
<td>Calcul. Creatine clear.</td>
</tr>
<tr>
<td>Blood Chemistry</td>
</tr>
<tr>
<td>Hematology</td>
</tr>
<tr>
<td>Urinalysis</td>
</tr>
<tr>
<td>WHO toxicity grading</td>
</tr>
</tbody>
</table>

- **Abbreviations**: Cycle 0 = baseline; R = rest week; WHO = World Health Organization.
- Baseline creatinine clearances should be calculated using the Cockcroft and Gault formula [Attachment 6] (for dose adjustments see 3.6.2.2.4., Table 7).
- Blood chemistry: bilirubin, alkaline phosphatase, ALT and AST, BUN, creatinine, calcium, total protein, albumin, sodium and potassium, lactic dehydrogenase (LDH).
- Hematology: Full blood count (FBC) (hemoglobin, white blood cells [WBC], neutrophils, platelets).

**General considerations:**

- Study drug should be given as stipulated, but may be given within a window of 2 days if circumstances dictate this (i.e. holidays etc. 3.6.2.1.). No new cycle of Gemcitabine should start unless the absolute leucocyte count is ≥3.5 x10^9/L and the platelet count is ≥100 x10^9/L taken within 24 hours prior to therapy. Doses held due to toxicity or missed will not be given at a later time. If the dose held or missed was to be given on day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient (i.e., 1-2-R, X-1-2-R, etc). If the second (day 8) dose is held or missed, the cycle would continue per protocol with one dose not given (ie, 1-2-R, 1-X-R, etc). The following week a dose would be administered (if toxicity permits) and considered the beginning (day 1) of a new cycle. A patient who cannot be administered drug for 4 weeks from the time of the last study drug administration must be discontinued from the study unless approved by the principal investigator (3.6.2.2.2.).
- In case of minor pulmonal, cutaneous, allergic or fever toxicities use of three times dexamethason 8mg (just before the scheduled Gemcitabine infusion, as well as 12 and 24 hours after infusion) should be considered.
## Attachment 3b: Followup Schedule

<table>
<thead>
<tr>
<th>Months after end of adjuv. Chemotherapy Arm A</th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
<th>16 mo</th>
<th>20 mo</th>
<th>24 mo</th>
<th>30 mo</th>
<th>36 mo</th>
<th>42 mo</th>
<th>48 mo</th>
<th>54 mo</th>
<th>60 mo</th>
<th>72 mo</th>
<th>84 mo</th>
<th>96 mo</th>
<th>108 mo</th>
<th>120 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>aChest X-Ray</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>aAbd. CT or MRI Scan</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weeks/Months after radical operation Arm B</th>
<th>6 wks</th>
<th>12 wks</th>
<th>18 wks</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
<th>16 mo</th>
<th>20 mo</th>
<th>24 mo</th>
<th>30 mo</th>
<th>36 mo</th>
<th>42 mo</th>
<th>48 mo</th>
<th>54 mo</th>
<th>60 mo</th>
<th>72 mo</th>
<th>84 mo</th>
<th>96 mo</th>
<th>108 mo</th>
<th>120 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>aChest X-Ray</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>aAbd. CT or MRI Scan</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

### Weeks after radical operation ArmA /ArmB

<table>
<thead>
<tr>
<th>4 wks</th>
<th>12 wks</th>
<th>24 wks</th>
<th>36 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>bQOL assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Abbreviations:** wks = weeks; mo = months; CT = Computerized Tomography; MRI = Magnetic Resonance Imaging; QOL = Quality of life

- Any patients from Arm B requiring confirmation of response after administration of the drug for progression will have this done by the same methodology as used previously.
- QOL assessment during the study is synchronized for the two arms, so QOL assessment is independent of study drug administration.
Attachment 4:  
Recommendations for Reporting of Serious Adverse Events

When telephoning the Principal Investigator or the manufacturer of the drug (Lilly Deutschland GmbH) to report a serious adverse event, please have the following information available:

Patient Demographics
- patient identification (number)
- sex
- date of birth
- race

Study Identification
- protocol number
- investigator's name

Test Drug
- drug code or drug name
- unit dose
- total daily dose
- frequency
- route
- start dose

Adverse Event
- description
- date of onset
- severity
- treatment (including hospitalisation)
- action taken with respect to test drug
- clinical significance
- test results (if applicable)

Relationship to Test Drug

Concomitant Drug Therapy
- indication
- total daily dose
- duration of treatment

In Case of Death
- cause
- autopsy findings (if available)
## Attachment 5a:

### WHO Recommendations for Grading of Acute and Subacute Toxicity (Hematologic)

<table>
<thead>
<tr>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic (Adults)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g/100 mL</td>
<td>≥ 11.0</td>
<td>9.5 - 10.9</td>
<td>8.0 - 9.4</td>
<td>6.5 - 7.9</td>
<td>&lt;6.5</td>
</tr>
<tr>
<td>g/L</td>
<td>≥ 110</td>
<td>95 - 109</td>
<td>80 – 94</td>
<td>65 – 79</td>
<td>&lt;65</td>
</tr>
<tr>
<td>mmol/L</td>
<td>≥ 6.8</td>
<td>5.8 - 6.7</td>
<td>4.95 - 5.8</td>
<td>4.0 - 4.9</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>Leucocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^3/mm^3</td>
<td>≥ 4.0</td>
<td>3.0 - 3.9</td>
<td>2.0 - 2.9</td>
<td>1.0 - 1.9</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Granulocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^3/mm^3</td>
<td>≥ 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^3/mm^3</td>
<td>≥ 100</td>
<td>75 - 99</td>
<td>50 – 74</td>
<td>25 – 49</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td>petechiae</td>
<td>mild blood loss</td>
<td>gross blood loss</td>
<td>debilitating blood loss</td>
</tr>
</tbody>
</table>

Approved by Lilly: 16 February 2000
### Attachment 5b

**WHO Recommendations for Grading of Acute and Subacute Toxicity**  
(***Gastrointestinal***)

<table>
<thead>
<tr>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>≤1.25 x N⁺</td>
<td>1.26 - 2.5 x N⁺</td>
<td>2.6 - 5 x N⁺</td>
<td>5.1 - 10 N⁺</td>
<td>&gt;10 x N⁺</td>
</tr>
<tr>
<td>Transaminases (AST/ALT)</td>
<td>≤1.25 x N⁺</td>
<td>1.26 - 2.5 x N⁺</td>
<td>2.6 - 5 x N⁺</td>
<td>5.1 - 10 N⁺</td>
<td>&gt;10 x N⁺</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>≤1.25 x N⁺</td>
<td>1.26 - 2.5 x N⁺</td>
<td>2.6 - 5 x N⁺</td>
<td>5.1 - 10 N⁺</td>
<td>&gt;10 x N⁺</td>
</tr>
<tr>
<td>Oral</td>
<td>none</td>
<td>soreness/erythema</td>
<td>erythema, ulcers; can eat solids</td>
<td>ulcers; requires liquid diet only</td>
<td>alimentation not possible</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>none</td>
<td>nausea</td>
<td>transient vomiting</td>
<td>vomiting requiring therapy</td>
<td>Intractable vomiting</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>none</td>
<td>transient, &lt;2days</td>
<td>tolerable, but &gt;2 days</td>
<td>intolerable, requiring therapy</td>
<td>Hemorrhagic Dehyderation</td>
</tr>
</tbody>
</table>

aN= upper limit of normal
### Attachment 5c

**WHO Recommendations for Grading of Acute and Subacute Toxicity**

<table>
<thead>
<tr>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>≤1.25 x N&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.26 - 2.5 x N&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.6 - 5 x N&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 - 10 N&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;10 x N&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>or Serum creatinine</td>
<td>none</td>
<td>1+</td>
<td>2 - 3+</td>
<td>4+</td>
<td>4+ nephrotic syndrome</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>none</td>
<td>&lt;0.3 g%</td>
<td>0.3 - 1.0 g%</td>
<td>&gt;1.0 g%</td>
<td>&gt;10 g/L obstructive uropathy</td>
</tr>
<tr>
<td>Hematuria</td>
<td>none</td>
<td>microscopic</td>
<td>gross</td>
<td>gross plus clots</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>none</td>
<td>mild symptoms</td>
<td>exertional dyspnea</td>
<td>dyspnea at rest</td>
<td>complete bed rest required</td>
</tr>
<tr>
<td>Fever with Drug</td>
<td>none</td>
<td>fever &lt;38°C</td>
<td>fever 38° - 40°C</td>
<td>fever &gt;40°C</td>
<td>fever with hypotension</td>
</tr>
<tr>
<td>Allergic</td>
<td>none</td>
<td>Edema</td>
<td>bronchospasm; no parenteral therapy needed</td>
<td>bronchospasm; parenteral therapy required</td>
<td>anaphylaxis</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>none</td>
<td>Erythema</td>
<td>dry desquamation, vesiculation, pruritus</td>
<td>moist desquamation, ulceration</td>
<td>exfoliative dermatitis, necrosis requiring surgical intervention</td>
</tr>
<tr>
<td>Hair</td>
<td>none</td>
<td>minimal hair loss</td>
<td>Moderate, patchy Alopecia</td>
<td>complete alopecia but reversible</td>
<td>nonreversible alopecia</td>
</tr>
</tbody>
</table>

<sup>a</sup>N= upper limit of normal

Approved by Lilly: 16 February 2000
### Attachment 5d

**WHO Recommendations for Grading of Acute and Subacute Toxicity**  
*(Neurotoxicity/Pain)*

<table>
<thead>
<tr>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurotoxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State of consciousness</td>
<td>alert</td>
<td>Transient lethargy</td>
<td>somnolence &lt;50% of waking hours</td>
<td>somnolence &lt;50% of waking hours</td>
<td>coma</td>
</tr>
<tr>
<td>Peripheral</td>
<td>none</td>
<td>Paresthesias and/or decreased tendon reflexes</td>
<td>severe paresthesias and/or mild weakness</td>
<td>intolerable paresthesias and/or marked motor loss</td>
<td>paralysis</td>
</tr>
<tr>
<td>Constipation(^b)</td>
<td>none</td>
<td>mild</td>
<td>moderate</td>
<td>abdominal distention</td>
<td>distention and vomiting</td>
</tr>
<tr>
<td><strong>Pain(^c)</strong></td>
<td>none</td>
<td>Mild</td>
<td>moderate</td>
<td>severe</td>
<td>intractable</td>
</tr>
</tbody>
</table>

\(^b\)Does not include constipation resulting from narcotics  
\(^c\)Pain - only treatment-related pain is considere, not disease-related pain. The use of narcotics may be helpful in grading pain depending upon the tolerance level of the patient.
## Attachment 5e

**WHO Recommendations for Grading of Acute and Subacute Toxicity**  
*(Neurotoxicity Hearing)*

<table>
<thead>
<tr>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotoxicity</td>
<td>none or no change</td>
<td>asymptomatic hearing loss on audiometry only</td>
<td>tinnitus</td>
<td>Hearing loss interfering with function but correctable with hearing aid</td>
<td>deafness not correctable</td>
</tr>
<tr>
<td>Neurohearing *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Attachment 5f

## WHO Recommendations for Grading of Acute and Subacute Toxicity (Infection/Cardiac)

<table>
<thead>
<tr>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td>none</td>
<td>Minor infection</td>
<td>Moderate infection</td>
<td>major infection</td>
<td>major infection with hypotension</td>
</tr>
<tr>
<td>(specify site)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Rhythm</strong></td>
<td>none</td>
<td>Sinus tachycardia</td>
<td>Unifocal PVC, atrial</td>
<td>multifoal PVC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 110 at rest</td>
<td>Arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Function</strong></td>
<td>none</td>
<td>asymptomatic, but</td>
<td>Transient Symptomatic</td>
<td>symptomatic dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>abnormal cardiac</td>
<td>Dysfunction; no Therapy</td>
<td>responsive to therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>sign</td>
<td>required</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pericarditis</strong></td>
<td>none</td>
<td>asymptomatic</td>
<td>Symptomatic; no Tap</td>
<td>tamponade; tap required</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>effusion</td>
<td>required</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Attachment 6:
Calculating Creatinine Clearance

Cockcroft and Gault Formula [Cockcroft and Gault, 1976]

Male: \([140 - \text{age}] \times \text{weight (kg)} / \text{[72 x serum creatinine (mg/dL)]} = \text{mL/min.}\)
Female: \([140 - \text{age}] \times 0.85 \times \text{weight (kg)} / \text{[72 x serum creatinine (mg/dL)]} = \text{mL/min}\)

*Serum creatinine conversion factors: 0.0113 mol/L = 11.3 mmol/L = 1.0 mg/dL*
Attachment 7:

EORTC QLQ-C30 (Version 2.0)-Fragebogen

Wir möchten Ihnen einige Fragen stellen, die Ihr Wohlbefinden und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am ehesten auf Sie zutrifft. Es gibt keine “richtigen” oder “falschen” Antworten. Ihre Angaben werden streng vertraulich behandelt.

1. Bereitet es Ihnen Schwierigkeiten, sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen?)
2. Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?
3. Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?
4. Müssen Sie den größten Teil des Tages im Bett oder in einem Sessel verbringen?
5. Brauchen Sie Hilfe beim Essen, Anziehen, Waschen, oder Benutzen der Toilette?

Die folgenden Fragen beziehen sich auf die letzte Woche:

6. Waren Sie bei Ihrer Arbeit oder bei anderen tätigen Beschäftigungen eingeschränkt?
7. Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?
8. Waren Sie kurzatmig?
9. Hatten Sie Schmerzen?
10. Mußten Sie sich ausruhen?
11. Hatten Sie Schlafstörungen?
12. Fühlten Sie sich schwach?
13. Hatten Sie Appetitmangel?
14. War Ihnen übel?
15. Haben Sie erbrochen?
16. Hatten Sie Verstopfung?
17. Hatten Sie Durchfall?
18. Waren Sie müde?
19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?
Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft:

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

Sehr schlecht ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

Sehr schlecht ausgezeichnet

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Attachment 8: Protocol Signatures

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my agreement with the principal investigator.

Instructions to the investigator--Please SIGN and DATE both copies of this signature page. PRINT your name, title, and the name of the facility in which the study will be conducted on both copies. Return one of the signed copies to the principal investigator.

________________________________ ___________ ___ ________________________________ _
Signature of Investigator Date
Attachment 9 (Revised March 17, 2000):
Patient Information & Informed Consent Form

Adjuvante vs. progressionsabhängige Chemotherapie mit Gemcitabin (Gemzar\textsuperscript{®}) nach radikaler Zystektomie bei lokal fortgeschrittenem Harnblasenkarzinom bei Patienten, die für eine Cisplatinhaltige Chemotherapie nicht geeignet sind

Patienteninformation

Sehr geehrte Patientin, sehr geehrter Patient,

wie Sie wissen, liegt bei Ihnen eine bösartige Erkrankung der Harnblase vor. Diese Krebserkrankung ist bereits behandelt worden, indem Sie eine radikale Operation der Harnblase erhalten haben. Allerdings ist diese Therapie möglicherweise nicht ausreichend, um Ihre Krebserkrankung heilen zu können.

In dieser Situation gibt es zur Zeit leider keine Standardtherapie, die Aussicht auf vollständige Heilung hat. Als weitere zusätzliche Behandlungsmöglichkeit bieten wir Ihnen, im Rahmen einer klinischen Studie, den Einsatz einer Chemotherapie an.

Bevor Sie Ihre Einwilligung zur Teilnahme geben, ist es wichtig, daß Sie das Ziel der Studie und die Behandlungen und Untersuchungen, die durchgeführt werden, kennen.

Weiterhin informieren wir Sie über die Vorteile und möglichen Belastungen und Risiken, die mit Ihrer Teilnahme an der Studie verbunden sein können.


Als Nebenwirkungen unter der Behandlung mit Gemzar\textsuperscript{®} können u. a. die unten aufgezählten Symptome auftreten. Viele dieser Nebenwirkungen sind nur in sehr seltenen Fällen beobachtet worden, in anderen Fällen sind sie als unvermeidbare Nebenwirkungen einer jeden Chemotherapie anzusehen.
Bekannte Nebenwirkungen von Gemzar\textsuperscript{®} können sein: Abnahme der weißen Blutkörperchen, der Thrombozyten und roten Blutkörperchen (Anämie). Effekte auf den Magen-Darm-Trakt beinhalten Übelkeit, Übelkeit mit Erbrechen (Übelkeit und Erbrechen führen aber nur selten zu Therapieabbruch einer Behandlung mit Gemzar\textsuperscript{®} und können durch Verabreichung begleitender Medikamente kontrolliert und reduziert werden). Leberfunktionsstörungen sind meist leicht (z.B. nicht fortschreitende Änderungen bei Leberfunktionsstests, die selten zum Therapieabbruch führen). Es können auch leichte Auswirkungen auf die Nieren beobachtet werden (Eiweiß oder Blut im Urin). Weitere häufiger vorkommende Nebenwirkungen können sein: Fieber, Schüttelfrost, Kopfschmerzen, Muskelläden und Abnahme des Appetits (fieberähnliche Symptome); Husten, Schnupfen, Schwitzen, Hautausschlag, geringer Haarausfall, Flüssigkeitsstau, Kurzatmigkeit, Verstopfung und Schwäche.


Die beschriebenen Begleitwirkungen bilden sich nach Beendigung der Therapie in der Regel zurück.


Sie werden dem Zufall entsprechend dem einen oder anderen Arm zugeteilt, ohne dass dies nach den vorliegenden Daten Nachteile in Bezug auf das Tumoransprechen für Sie zur Folge hat. Falls sich zeigt, daß im Arm B (abwartende Strategie) Patienten ein Wiederauftreten der Tumorerkrankung entwickeln, werden diese Patienten sofort eine Therapie mit Gemzar\textsuperscript{®} nach dem gleichen Muster wie Patienten im Arm A erhalten.

Im Behandlungsarm A der Studie wird Gemzar\textsuperscript{®} innerhalb von 3 Wochen jeweils über 30 Minuten an zwei einzelnen Tagen (Tag 1 und 8) durch eine Vene gegeben. Dies kann ambulant erfolgen und bedarf häufig keiner stationären Aufnahme. Ein Zyklus beträgt 3 Wochen und soll bis zu 6 Mal wiederholt werden. Die wiederholte Gabe ist vom Erfolg der Therapie abhängig. Schreitet die Erkrankung während der Therapie fort, wird die Therapie abgebrochen und es kann eventuell der Wechsel auf andere Behandlungsformen erfolgen.

Vor Behandlungsbeginn und während der Behandlung werden gründliche ärztliche Untersuchungen durchgeführt. Zu Ihrer Sicherheit wird Ihr Blut untersucht, um mögliche Nebenwirkungen festzustellen. Ebenso werden in regelmäßigen Abständen bildgebende Verfahren (Computertomographie und Röntgen) durchgeführt. Die Häufigkeit der Blutuntersuchungen und das Volumen des abgenommenen Blutes, sowie die Röntgenuntersuchungen entsprechen von Art und Häufigkeit dem üblichen Nachsorgeschema nach Radikaloperationen. Es werden also keine Röntgenuntersuchungen empfohlen, die nur dem Zweck dieser Studie dienen. Vor jedem
Behandlungszyklus werden Ihre Beschwerden dokumentiert und eine körperliche Untersuchung durchgeführt.
Nach Therapieende erfolgt eine regelmäßige Nachsorge im 3-monatlichen Abstand im ersten Jahr, 4-monatlichen Untersuchungen im zweiten Jahr, 6-monatigen Untersuchungen im dritten bis fünften Jahr und anschließend jährliche Abstand. Auch diese Untersuchungen würden man außerhalb einer Studie bei Ihnen empfehlen.
Sollten sie keine Chemotherapie erhalten, da Sie dem Behandlungsarm B zugewiesen wurden und bei Ihnen kein Tumor wiederauftritt, erfolgt die Nachsorge ebenfalls wie oben beschrieben mit 3-monatlichen Untersuchungen im ersten Jahr, 4-monatlichen Untersuchungen im zweiten Jahr, u.s.w.)
Bitte beachten Sie, daß die gleichzeitige Einnahme von anderen Arzneimitteln die Wirkung der Studienmedikamente beeinflussen kann. Aus diesem Grund sollten Sie Ihren Arzt über alle (auch nicht rezeptpflichtigen) Medikamente, die Sie im Verlauf der Studie einnehmen, genau informieren.
Die Teilnahme an dieser Studie ist vollständig freiwillig und es besteht jederzeit die Möglichkeit, die Teilnahme an dieser Studie ohne Angaben von Gründen zu widerrufen. Es entstehen Ihnen im Falle einer solchen Entscheidung keinerlei Nachteile für die weitere Behandlung und Therapie. Sie haben die Möglichkeit, zu jeder Zeit mit den verantwortlichen Ärzten dieses Projektes über den Fortgang der Behandlung zu sprechen.
Vertraulichkeit


Sie willigen ein, daß die beteiligten Ärzte an dieser klinischen Prüfung alle Aufzeichnungen von Krankheitsdaten in Zusammenhang mit Ihrer Studienteilnahme an die Lilly Deutschland GmbH einschließlich deren Vertreter und Auftragnehmer, die zuständige Überwachungsbehörde, und/oder die zuständige Bundesoberbehörde weitergeben dürfen.

Außerdem erklären Sie sich einverstanden, daß zur Kontrolle der Prüfergebnisse zur Verschwiegenheit verpflichtete Mitarbeiter der Fa. Lilly Deutschland GmbH, einschließlich deren Auftragnehmer oder autorisierter Personen obengenannter Behörden, Einsicht in Ihre Krankenakte nehmen.

Ihr behandelnder Arzt wird dabei darauf achten, daß sich die Einsicht in Ihre Krankenakte auf das zur Kontrolle der Studie erforderliche Maß beschränkt, die personenbezogenen Daten streng vertraulich behandelt und nur in anonymisierter Form weitergegeben werden.

Versicherungsschutz

Nach den Bestimmungen des Arzneimittelgesetzes (§ 40 AMG) muß für jeden Teilnehmer an einer klinischen Prüfung eine Probanden-/Patienten-Versicherung abgeschlossen werden.

Deshalb besteht für Sie ein Versicherungsschutz bei der Colonia Versicherungs AG, Filialdirektion Frankfurt/Main (Tel: 069 – 977501), Probanden-Versicherungsnummer 60 22 60 10202, mit einer Höchstgrenze von DM 1.000.000,-- (eine Million) für den Fall einer Gesundheitsschädigung, die als Folge der Anwendung von Arzneimitteln oder von Maßnahmen an Ihrem Körper in Zusammenhang mit der klinischen Prüfung entstanden ist.

Um Ihren Versicherungsschutz nicht zu verlieren, dürfen Sie sich einer anderen medizinischen Behandlung während der Dauer der klinischen Prüfung - außer in Notfällen - nur nach Absprache mit Ihrem Arzt unterziehen. Eine Gesundheitsschädigung, die als Folge der klinischen Prüfung eingetreten sein könnte, ist der Versicherung nach Rücksprache mit Ihrem Arzt unverzüglich anzuzeigen. Sie oder Ihr Arzt können sich in einem solchen Fall direkt an die Colonia Versicherung AG, Filialdirektion Frankfurt/Main, oder an die Lilly Deutschland GmbH, die Ihnen als Kooperationspartnen der Studie gerne behilflich ist, wenden.
Studientitel:
Adjuvante vs. progressionsabhängige Chemotherapie mit Gemcitabin (Gemzar®) nach radikaler Zystektomie bei lokal fortgeschrittenem Harnblasenkarzinom bei Patienten, die für eine Cisplatinhaltige Chemotherapie nicht geeignet sind

Einverständniserklärung

Mir wurde die Patienteninformation zur Behandlungstudie mit Gemzar® und ausgehändigt und ich habe sie sorgfältig gelesen.

Dr.med....................

Anschrift...................................................

Telefon....................


........  ..................
Datum     Unterschrift Patient

........  ..................
Datum     Unterschrift Prüfarzt
Adjuvant Gemcitabine for Locally Advanced Bladder Cancer

Approved by Lilly: 16 February 2000

Randomize

Arm A (immediate treatment)
start therapy up to 3 months after operation
(within 6 weeks postoperatively preferred)
QOL

or

Arm B (progression-triggered treatment)
no therapy unless progressive disease apparent
QOL

Gemcitabine\(^1\) 1250 mg/m\(^2\) iv over 30 min, day 1 and 8
Repeat cycle every 21 days maximum of 6 cycles

Follow on observation until relapse or progression.
(Primary endpoint)

Follow on observation until death.
(Secondary endpoint)

Gemcitabine\(^1\) 1250 mg/m\(^2\) iv over 30 min, day 1 and 8
Repeat cycle every 21 days maximum of 6 cycles

Total accrual = 178 patients (89 patients in each arm), estimated annual accrual = 60 patients

\(^1\) At the beginning of each cycle, use patient’s actual weight when calculating doses

\(^2\) QOL assessment at 4 timepoints: 4 weeks, 12 weeks, 24 weeks and 36 weeks after radical operation.