Organ-Sparing Treatment of Advanced Bladder Cancer

Paclitaxel as a Radiosensitizer

Arndt-Christian Müller[1, 2], Andrea Diestelhorst[1], Thomas Kuhnt[1], Reinhard Kühn[3], Paolo Fornara[4], Hans-Jörg Scholz[5], Jürgen Dunst[1, 6], Anthony Laurence Zietman[7]

Background and Purpose: Transurethral resection of bladder tumor (TUR-BT) and radiochemotherapy with cisplatin achieve high rates of bladder preservation and survival figures identical to radical cystectomy in muscle-invasive bladder cancers. The authors have investigated the potential use of paclitaxel in a radiochemotherapy protocol for patients with inoperable bladder carcinomas and mainly contraindications to cisplatin.
Patients and Methods: Between October 1997 to August 2004, 42 patients (median age 71 years) suffering from muscle-invasive (n = 32) or recurrent (n = 10) bladder cancers were treated with a paclitaxel-containing radiochemotherapy (paclitaxel 25–35 mg/m^2 twice weekly) after TUR-BT (R0/1/2/x in n = 18/4/14/3) or cystectomy with residual tumor (n = 3). Five patients received additional cisplatin. Radiation treatment was administered to a total dose of 45–60 Gy.
Results: 76.2% completed the planned regimen. Adaptations of treatment were mainly required due to diarrhea. Grade 3/4 toxicities occurred in 15/1 patients. Severe renal toxicities did not occur. 28 patients underwent restaging TUR-BT 6 weeks after radiochemotherapy (complete remission/partial remission/progressive disease: n = 24/3/1). Three patients developed a local recurrence and four distant metastases. Seven patients died from tumor, six of other reasons.
Conclusion: Radiochemotherapy with paclitaxel was feasible and this bladder approach needs further investigation to evaluate whether paclitaxel could become a substitute for cisplatin.

Key Words: Bladder cancer · Radiotherapy · Chemotherapy · Bladder preservation

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Organerhaltende Behandlung bei fortgeschrittenen Harnblasenkarzinomen. Paclitaxel als Radiosensitizer

Hintergrund und Ziel: Bei muskelinvasiven Harnblasenkarzinomen erreicht die transurethrale Resektion (TUR-B), gefolgt von einer Radiochemotherapie mit Cisplatin, zu einem hohen Prozentsatz den Blasenerhalt und vergleichbare Überlebensdaten wie die radikale Zystektomie. Die Autoren untersuchten bei Patienten mit inoperablen Harnblasenkarzinomen und Kontraindikationen für Cisplatin den möglichen Stellenwert eines Paclitaxel-basierten Radiochemotherapieprotokolls.
Patienten und Methodik: Von Oktober 1997 bis August 2004 wurden 42 Patienten (medianes Alter von 71 Jahren) mit muskelinvasiven (n = 32) oder rezidivierten (n = 10) Blasenkarzinomen mit einer Paclitaxel-haltigen Radiochemotherapie (Paclitaxel 25–35 mg/m^2 zweimal wöchentlich) nach TUR-B (R0/1/2/x bei n = 18/4/14/3) oder unradikaler Zystektomie (n = 3) behandelt. Fünf Patienten erhielten zusätzlich Cisplatin. Die Radiotherapie wurde bis zu einer Gesamtdosis von 45–60 Gy appliziert.
Ergebnisse: 76,2% der Patienten beendeten wie geplant das Protokoll. Abweichungen waren hauptsächlich wegen Diarrhö erforderlich. Grad-3/4-Akuttoxizitäten waren bei 15/1 Patienten zu verzeichnen. Schwerwiegende renale Toxizitäten traten nicht auf. Bei 28 Patienten wurde eine Kontroll-TUR-B 6 Wochen nach der Radiochemotherapie durchgeführt (komplette Remission/partielle Remission/Krankheitsprogress: n = 24/3/1). Bei drei Patienten traten Lokalrezidive und bei vier Patienten Fernmetastasen auf. Sieben Patienten verstarben tumorbedingt, sechs aus anderen Gründen.
Schlussfolgerung: Die Radiochemotherapie mit Paclitaxel war in diesem Konzept durchführbar. Weitere Untersuchungen sind erforderlich, um Paclitaxel als Alternative zu Cisplatin zu evaluieren.

Schlüsselwörter: Harnblasenkarzinom · Radiotherapie · Chemotherapie · Blasenerhalt

[1] Department of Radiation Oncology, University of Halle, Germany,
[2] Department of Radiooncology, University of Tübingen, Germany,
[3] Department of Urology, Martha Maria Hospital Halle, Germany,
[4] Department of Urology, University of Halle, Germany,
[5] Department of Urology, Asklepios Hospital Weißenfels, Germany,
[6] Department of Radiation Oncology, University of Lübeck, Germany
[7] Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

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Introduction

Bladder cancer is the fifth most commonly occurring malignancy in the developed countries with approximately 15,000 new cases diagnosed in Germany every year. 80% are superficial and mainly treated by transurethral resection of the bladder tumor (TUR-BT) with or without intravesical therapy. The search for the optimal treatment of muscle-invasive bladder cancer (T2–T4) is still ongoing. The standard treatment is cystectomy despite encouraging results of organ-preserving regimens. The techniques of both surgery and radio(chemo)therapy have improved over the last 2 decades. And the question how best to treat an operable patient remains an important issue. No randomized trial has ever been performed to directly compare the two treatment approaches.

The choice of the curative treatment modality for muscle-invasive bladder cancer in patients unsuitable for radical surgery focuses on a different debate whether monotherapy or combined modalities offer the best chance for disease control. Published data suggests that less aggressive strategies do seem to be inferior. The complete response rates of protocols employing irradiation alone, chemotherapy alone, or TUR-BT plus chemotherapy did not reach the complete response rates of the multimodality approach with TUR-BT and radiochemotherapy (complete response rates of 45%, 27%, 51% vs. 71%) [24].

Paclitaxel is a radiosensitizer belonging to the class of taxanes. Radiation dose modification factors of 1.5–1.8 have been reported in clonogenic assays in four human cell lines [13]. Cells develop a cell-cycle arrest in the most radiosensitive phase (late G2/M) after paclitaxel explaining the synergism with radiation. In vitro investigations of Kugler et al. [12] with paclitaxel in human transitional cancer cells in comparison to the MVAC standard suggest that paclitaxel may be a clinically useful agent for systemic and intravesical use in bladder cancer. A case report about paclitaxel and irradiation [27] and a review about concurrent radiochemotherapy with paclitaxel and carboplatin in eight patients [17] reported promising results in bladder carcinomas. Paclitaxel has been shown to be effective in bladder cancer as single agent or in combination with other cytotoxic drugs [2, 9, 19, 25]. Our first radiochemotherapy results (seven patients) with concomitant paclitaxel in the late 1990s were promising [7].

In this series, we have investigated whether or not a radiochemotherapy regimen with a lower nephrotoxic profile would be both tolerable and effective in bladder cancer patients with either a contraindication to – or refusal of – radical cystectomy.

Table 1. Patient characteristics (n = 42).

Tabelle 1. Patientencharakteristika (n = 42).

Characteristic		Patients receiving radiotherapy plus paclitaxel n	%
Gender	Male	40	95.2
	Female	2	4.8
	Total	42	100.0
Age	Median	71 years	
	Range	42–80 years	
Karnofsky performance scale	90–100%	7	16.7
	70–80%	26	61.9
	50–60%	8	19.0
	30–40%	1	2.4
	Total	42	100.0

Table 2. Tumor characteristics (n = 42).

Tabelle 2. Tumorcharakteristika (n = 42).

Characteristic		Patients receiving radiotherapy plus paclitaxel n	%
T-category	T1	2	4.8
	T2	18	42.9
	T3	10	23.8
	T4	10	23.8
	Ta + Tis	1	2.4
	T1 + Tis	1	2.4
	Total	42	100.0
N-category	cN0/Nx	40	95.2
	cN+	2	4.8
	Total	42	100.0
Grading	G1	1	2.4
	G2	6	14.3
	G3	35	83.3
	Total	42	100.0
Residual tumor (R-classification) after TUR-BT/surgery	R0	18	42.9
	R1	4	9.5
	R2	14	33.3
	Rx	3	7.1
	Cystectomy with residual tumor	3	7.1
	Total	42	100.0

Patients and Methods

Patient Characteristics

From October 1997 through August 2004, 42 patients (40 males and two females) suffering from muscle-invasive (T2–T4) or high-risk T1 bladder cancer (G3 with/without Tis, multifocality, recurrences after TUR-BT) were treated with a paclitaxel-containing simultaneous radiochemotherapy (paclitaxel n = 37, paclitaxel and cisplatin n = 5). Chemo-irradiation was performed mainly after initial TUR-BT. TUR-BT achieved an R0 resection in 18 patients (42.9%), R1 in four (9.5%), R2 in 14 (33.3%), and Rx in three (7.1%). The remaining three patients (7.1%) were treated after cystectomy with residual tumor. Ten patients had severe hydronephrosis requiring unilateral (n = 8) or bilateral (n = 2) percutaneous nephrostomy. The treatment intent was curative in 40 patients (95.2%) and palliative in two cases (4.8%; Tables 1 and 2).

Treatment Schedule

Radiation therapy started within 4–8 weeks after maximal surgical reduction of tumor volume mainly by TUR-BT (39/42) or after cystectomy (with residual tumor) (3/42). Cross-sectional imaging studies (magnetic resonance imaging of pelvis or computed tomography of pelvis/abdomen) were performed before radiation treatment to assess the nodal involvement (Table 2). As described above, the decision for the type of simultaneous chemotherapy depended mainly on renal or cardiac function. The response was evaluated by TUR-BT 6–8 weeks after chemoirradiation. The organ-preserving treatment protocol is represented in Figure 1.

Radiotherapy

The bladder and the regional lymphatics were treated with 10- to 15-MV X-ray by a four-field box technique. A fractionated radiation dose (5 × 1.8–2 Gy/week to 45–50.4 Gy) was administered to the small pelvis and a boost (2-cm margin) with 1.8–2 Gy fraction size to 54–56 Gy (R0 TUR-BT) or 59.4–60 Gy (R1/2/x TUR-BT).

Simultaneous Chemotherapy

The paclitaxel-containing multimodality approach (TUR-BT + radiochemotherapy + restaging TUR-BT followed by salvage therapy, if necessary) was indicated when standard treatment, i.e., surgery or radiochemotherapy with cisplatin (Figure 2), was not applicable. The indication for paclitaxel was the contraindication for the cisplatin-based standard radiochemotherapy protocol in most cases (n = 37). Major reasons for contraindications to cisplatin were renal impairment, cardiac insufficiency, audiometrically proven inner ear hearing loss and refusion. Paclitaxel was administered twice weekly at a dose of 30 mg/m^2 after standard premedication during the whole radiation treatment (n = 30); four patients were treated with a reduced dose of paclitaxel (20 or 25 mg/m^2) and three patients with a higher dose (35 mg/m^2; Figure 2). In five other patients the constellation of young age, good Karnofsky performance status and a poor risk situation (R2, T4) has encouraged us to intensify the radiochemotherapy protocol containing the standard dose of cisplatin 25 mg/m^2 (days 1–5, 28–33) in weeks 1 and 5 [6] and paclitaxel 20/25/30 mg/m^2 twice weekly (n = 1/1/3) from week 2 to week 4.

Criteria for Response, Follow-up, Toxicity

The response was evaluated by deep TUR-BT 6–8 weeks after chemoirradia-

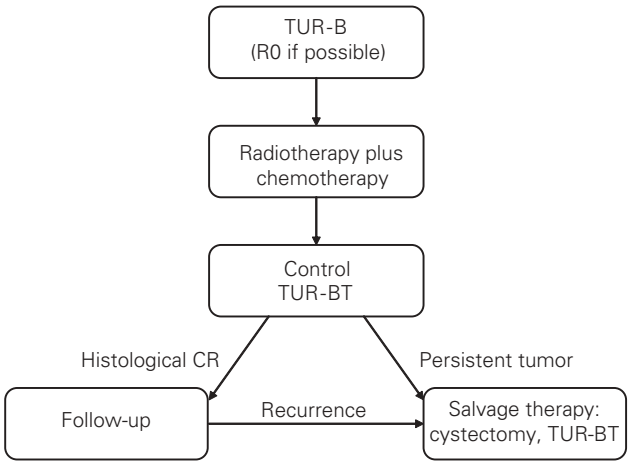

Figure 1. Treatment protocol: Radiation therapy started within 4–8 weeks after maximal surgical reduction of tumor volume mainly by TUR-BT (39/42) or after cystectomy (with residual tumor) (3/42). The response was evaluated by a control TUR-BT (in curative candidates) and the subsequent therapy depended on the histological result. Only in patients suitable for surgery a salvage cystectomy was possible (most patients in this investigation were unsuitable for surgery). Bladder preservation needs a lifelong follow-up.

Abbildung 1. Behandlungsprotokoll: Die Radiotherapie begann 4–8 Wochen nach maximaler chirurgischer Tumorreduktion mittels TUR-B (39/42) oder nach nicht radikaler Zystektomie (3/42). Das Ansprechen wurde mit einer Kontroll-TUR-B bei kurativem Ziel überprüft. Die weitere Therapie richtete sich nach dem histologischen Ergebnis. Nur bei operationsfähigen Patienten war eine Salvage-Zystektomie möglich. Die meisten Patienten waren jedoch nicht für eine Zystektomie geeignet. Bei blasenerhaltender Therapie ist eine lebenslange Nachsorge erforderlich.

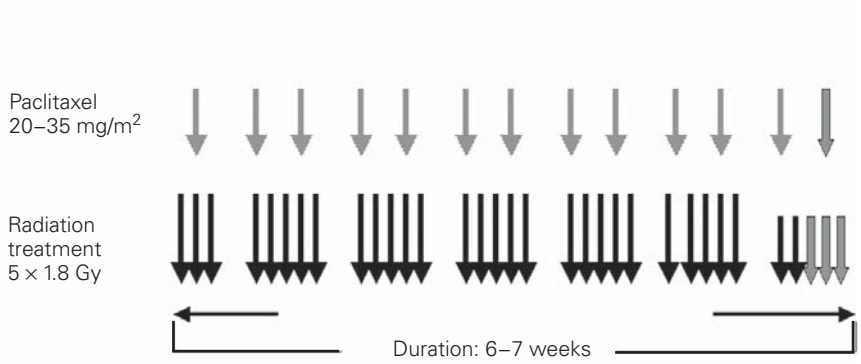

Figure 2. Paclitaxel was administered twice weekly at a dose of 20–35 mg/m^2 during the whole radiation treatment (n = 37). The intensified protocol given to a subgroup (n = 5) with poor risk and young age consisted of the standard dose of cisplatin 25 mg/m^2 (days 1–5) in weeks 1 and 5 and of paclitaxel 20–35 mg/m^2 twice weekly during the remaining radiation treatment time. A fractionated radiation dose (5 × 1.8 Gy/week to 45/50.4 Gy) was administered to the small pelvis and a boost with 1.8 Gy fraction size to 54–56 Gy (R0 TUR-BT) or 59.4–60 Gy (R1/2 TUR-BT).

Abbildung 2. Paclitaxel wurde zweimal wöchentlich in einer Dosis von 20–35 mg/m^2 während der Radiotherapie appliziert (n = 37). Bei einer Subgruppe (n = 5) mit hohem Risikoprofil und jungem Alter wurden Cisplatin in der Standarddosis von 25 mg/m^2 (Tage 1–5) in der 1. und 5. Behandlungswoche und zweimal wöchentlich Paclitaxel in einer Dosis von 20–35 mg/m^2 während der verbliebenen Radiotherapie gegeben. Die Radiotherapie wurde konventionell fraktioniert (5 × 1.8 Gy/Woche bis 45/50,4 Gy). Der Boost wurde in Abhängigkeit vom R-Status mit 1,8 Gy bis 54–56 Gy (R0-TUR-B) oder 59,4–60 Gy (R1/2-TUR-B) appliziert.

tion for curative treatments. If a palliative treatment (n = 2) was performed, no further surgical investigational procedure was initiated. In case of CR, patients were observed the first 2 years quarterly and half-yearly thereafter. Examinations consisted of medical history, physical examination, urine cytology, cystoscopy with biopsies, complete blood counts, and blood chemistry.

Salvage treatment was initiated for incomplete responders or in case of recurrence. Superficial tumors were treated by TUR-BT ± intravesical therapy (Figure 1). Salvage cystectomy was recommended for muscle-invasive tumors on condition that patients were suitable for surgery. We have used the Common Toxicity Criteria (CTC v2.0) since the year 2000 and converted earlier data to the CTC score [26]. Late toxicity was evaluated according to the grading system of Late Effects of Normal Tissues (LENT) [22].

Statistics

The median follow-up was 6 months (mean 9.6 months, range 1.4–45 months). The majority of the patients was recruited in the years 2003 and 2004 (Figure 3). So, the follow-up period was too short to calculate reliable annual rates for survival, disease- specific rates or late toxicity in this small study population.

Results

Therapy Compliance and Toxicity

The patients received a median total dose of 55.8 Gy (range 45–60 Gy). Median treatment time lasted 46 days (range 37–71 days; Table 3). 32 patients (76.2%) completed the planned radiotherapy and chemotherapy regimen as scheduled. Eight patients (19%) required adaptations or earlier termination of chemotherapy. One patient (2.4%) did not complete the radiotherapy, and in one patient (2.4%) both modalities were modified. The leading cause of protocol deviations was diarrhea (five patients, 11.9%). Other reasons (in one case each, i.e., 2.4%) were pneumonia, cardiac insufficiency, neutropenic fever, cystitis combined with diarrhea, and patient's desire.

Table 3. Treatment intent and protocol compliance.

Tabelle 3. Behandlungsintention und Compliance.

		Patients receiving radiotherapy plus paclitaxel	
		n	%
Treatment intent	Curative	40	95.2
	Palliative	2	4.8
Radiation treatment	Total dose	55.8 Gy ± 3.7 Gy	
	Range	45.0–60 Gy	
Chemotherapy regimen	Paclitaxel 20–35 mg/m²	37	88.1
	Paclitaxel and cisplatin	5	11.9
	Total	42	100.0
Median treatment time		46 days	
	Range	37–71 days	

Typical acute toxicities were transient cystitis, enteritis and radiation erythema easily managed by symptomatic treatment. 16 patients (38%) developed grade 1–2, ten (23.8%) grade 3, and one (2.4%) grade 4 diarrhea. Occasionally, nausea, vomiting and hematologic side effects, mainly grade 1 and 2, were present. Five patients received transfusions, one with erythropoietin and two erythropoietin only.

Serum creatinine remained in the reference range in 25 patients (59.5%). Grade 1–2 elevations were observed in nine patients (21.4%). In eight patients (19%), the creatinine value was elevated at the same level before and during the whole treatment. Severe renal toxicities requiring dialysis or unplanned hospitalization did not occur. An overview of acute toxicities manifesting at least of grade 2 is given in Table 4. The subgroup of patients treated only with irradiation and paclitaxel in curative intent without cystectomy is represented in brackets (n = 32).

Late toxicity was and is assessed, but our data are limited because of the short follow-up period (6-month median follow-up, Figure 3) due to the late recruitment of the majority of the patients in the last 3 years (32/42). In the period from the start of the study to August 2004, mild to moderate chronic enteritis (2/36) and cystitis (1/36) were evaluated. Bladder shrinkage was present in one patient.

Response

The response 6–8 weeks after chemoirradiation was evaluated by control TUR-BT in patients (28/42), who were candidates

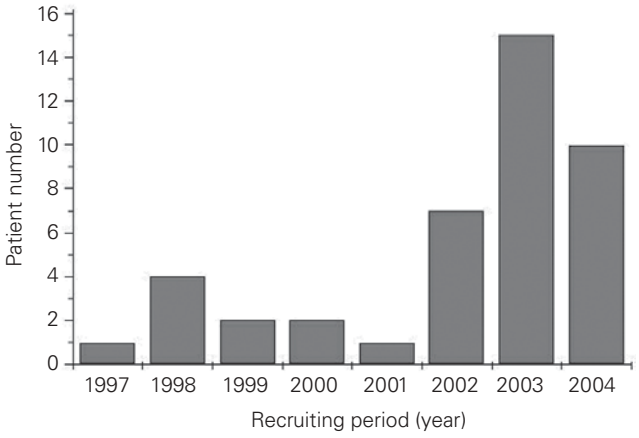

Figure 3. The recruitment period lasted from October 1997 to August 2004 (n = 42). Most patients were treated in the last 3 years (32/42). Consequently, the follow-up is mainly limited to a short period of investigation time.

Abbildung 3. Der Rekrutierungszeitraum reichte von Oktober 1997 bis August 2004 (n = 42). Die meisten Patienten wurden in den letzten 3 Jahren behandelt (32/42), weswegen der Nachbeobachtungszeitraum relativ begrenzt ist.

for salvage therapy (cystectomy or additional TUR-BT, Figure 1) and treated in curative intent (no metastasis, Karnofsky index ≥ 60% with a life expectancy > 6 months). The remaining patients (14/42) did not undergo a restaging TUR-BT for the listed reasons.

The response data of 28 patients (67%) are demonstrated in Table 5. 24 patients (24/28; 86% of performed restaging TUR-BTs) achieved a histologically proven complete remission and three a partial remission. One patient had early progressive disease. Five patients with TUR-BT and initial macroscopic residual disease (5/14) presented with a complete response 6 weeks after radiochemotherapy (35% of all R2 patients; 62.5% of all R2 candidates for salvage therapy, n = 8). Salvage cystectomies were performed in two patients suffering from recurring tumors.

Table 4. Acute toxicity of grade 2 or more. The frequency of acute toxicity of patients (n = 32) treated in curative intent, without cystectomy and without additional cisplatin, is demonstrated in brackets (i.e., acute toxicity restricted to radiochemotherapy with paclitaxel).

Tabelle 4. Akuttoxizität ab Grad 2. Zur alleinigen Beurteilung der Akuttoxizität von Radiochemotherapie mit Paclitaxel werden in Klammern die Akuttoxizitäten ausschließlich für kurativ behandelte Patienten ohne Zystektomie oder zusätzliche Cisplatin-Gabe dargestellt (n = 32).

CTC version 2.0	2	3	4	5
Anemia	7 (4)	–	–	–
Leukopenia	5 (3)	2 (1)	–	–
Thrombopenia	–	1 (0)	–	–
Creatinine[a]	4 (2)	–	–	–
Vomiting	2 (1)	–	–	–
Nausea	3 (1)	–	–	–
Radiation dermatitis	1 (0)	–	–	–
Urinary frequency	10 (6)	2 (2)	–	–
Diarrhea	12 (8)	10 (8)	1 (1)	

[a]Serum creatinine was elevated in eight patients before treatment and remained elevated at the same level after treatment explaining that these patients were not classified according to the Common Toxicity Criteria (CTC) score.

Table 5. Response evaluated by control TUR-BT after radiation treatment depending on initial R-stage (n = 28/42). The response of patients (22/32) treated in curative intent, without cystectomy and without additional cisplatin, is demonstrated in brackets (i.e., response restricted to radiochemotherapy with paclitaxel). CR: complete remission; PR: partial remission.

Tabelle 5. Der Therapieerfolg wurde durch eine Kontroll-TUR-B nach der Behandlung evaluiert und in Abhängigkeit vom initialen R-Stadium dargestellt (n = 28/42). Zur alleinigen Beurteilung des Ansprechens der Radiochemotherapie mit Paclitaxel werden in Klammern die Daten ausschließlich für kurativ behandelte Patienten ohne Zystektomie oder zusätzliche Cisplatin-Gabe dargestellt (22/32). CR: komplette Remission; PR: partielle Remission.

Radicality of initial TUR-BT	Response after radiochemotherapy CR	PR	Progression	Unknown[a]	Total
R0	12 (12)			6 (4)	18 (16)
R1	3 (3)			1 (1)	4 (4)
R2	5 (4)	2 (1)	1 (0)	6 (4)	14 (9)
Rx	2 (2)			1 (1)	3 (3)
Cystectomy	2 (0)	1 (0)			3 (0)
Total	24 (21)	3 (1)	1 (0)	14 (10)	42 (32)

[a] Control TUR-BT was not performed in 14 (10) patients due to limited salvage treatment options (comorbidity, patients after cystectomy), refusal, or palliative treatment.

Survival

Seven patients died from tumor, four of other reasons, one of intercurrent disease, and one of unknown causes (n = 13). 39 patients were alive in August 2004. Two of them had early progressive disease. Three patients developed a local recurrence and four distant metastases.

Discussion

The aim of this protocol was to investigate whether a potential curative radiochemotherapy regimen with a lower risk for nephrotoxicity than cisplatin is feasible and tolerable. It included patients with a variety of comorbidities. From a medical or tumor-related perspective, most of them were unsuitable for either radical cystectomy or curative radiochemotherapy with cisplatin. Negative prognostic factors like older age, hydronephrosis and reduced performance status were highly represented in this study population underlining the negative patient selection [8, 14, 16].

The treatment compliance (76.2%) and acute toxicity (Table 4) were equivalent to other chemoirradiation series [3, 5, 9, 10]. Grade 3 or 4 acute toxicities were observed in 16 patients (38%) and predominately caused by diarrhea (n = 11). Treatment-related deaths did not occur during radiochemotherapy. Compared with cisplatin-based regimens, diarrhea appeared more frequently with a paclitaxel-based protocol (Table 4, curatively treated paclitaxel group in brackets) but resolved with medication usually 2–4 weeks after treatment. Severe late complications were only present in one patient with bladder shrinkage.

Complete response, though only a surrogate parameter for the treatment success, is the essential condition for durable local control and bladder preservation. Complete response rate after R2 TUR-BT based on intent to treat was 44% (4/9) for patients treated only with paclitaxel in this protocol (one patient with partial response, in four patients no restaging TUR-BTs were performed). The complete response rate for all assessable patients was 86% (24/28 performed TUR-BTs). These encouraging response data are comparable with a cisplatin-containing radiochemotherapy [3, 6, 10]. By contrast, irradiation alone after TUR-BT achieves a complete response rate of approximately 45% [11, 14, 18].

Other bi- or trimodal bladder-sparing protocols like TUR-BT plus radiotherapy with or without concurrent carboplatin had not led to equivalent response rates like a cis-

platin-containing multimodal regimen in urothelial carcinomas (complete response rate after TUR-BT for radiotherapy alone: 61%; radiotherapy + carboplatin: 66%; radiotherapy + cisplatin: 82%; radiotherapy + cisplatin and 5-fluorouracil: 87%) [20, 21]. The question, whether irradiation plus cisplatin is superior to irradiation alone, was only addressed by one randomized trial. This Canadian study [4] demonstrated a significant advantage in local control for the combined-modality approach in T2–4b bladder cancers although this benefit did not contribute to an increased survival (3-year overall survival of 47% for radiochemotherapy with cisplatin vs. 33% for irradiation alone; not significant). It helped to establish cisplatin-based concurrent radiochemotherapy as the standard bladder-sparing alternative to cystectomy. New strategies like the sensitization of radioresistant cells by tumor necrosis factor-(TNF-)α or TNF-α-related apoptosis-inducing ligand (TRAIL) [15] could become an interesting additional treatment modality, since currently TNF-α proved supraadditivity with irradiation in bladder cancer cells [1].

Salvage cystectomy has a curative potential in patients with failure after radio(chemo)therapy. In our patients, however, only two salvage cystectomies were performed due to invasive recurrences despite the fact that salvage cystectomy was part of the treatment concept. This low frequency of salvage surgery, therefore, underlines the negative selection of patients for paclitaxel chemotherapy and will ultimately be reflected in lower 3- and 5-year survival rates. Future investigations should – besides the optimization of the bladder-preserving approach – integrate molecular markers to individualize the treatment decision [23, 28].

Conclusion

Radiochemotherapy with paclitaxel was feasible in this high-risk group with adverse prognostic factors. The toxicity profile, especially with regard to renal toxicity, suggests that paclitaxel might be an alternative to cisplatin, particularly in patients with contraindications to cisplatin. The pathologic response rate was encouraging in this series. However, additional follow-up will be required to determine whether or not these response rates translate into a comparable outcome to that achieved by chemoirradiation with cisplatin.

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Address for Correspondence
Dr. Arndt-Christian Müller
Klinik für Radioonkologie
Eberhard-Karls-Universität Tübingen
Hoppe-Seyler-Straße 3
72076 Tübingen
Germany
Phone (+49/7071) 29-85977, Fax -4682
e-mail: Arndt-Christian.Mueller@med.uni-tuebingen.de