Pelvic chemoradiotherapy after chemotherapy for metastatic bladder cancer

Kavitha Passaperuma, BSc,[1] Robert Ash MD,[2] Varugar Venkatesan, MB,[2] George Rodrigues, MD,[2] Eric Winquist, MD[3]

[1]Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada

[2]Division of Radiation Oncology, Department of Oncology, University of Western Ontario and London Health Sciences Centre, London, Ontario, Canada

[3]Division of Medical Oncology, Department of Oncology, University of Western Ontario and London Health Sciences Centre, London, Ontario, Canada

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Objective: *Consolidative radiotherapy has improved local control in other tumors with high local recurrence rates but has not been well studied in urothelial cancer. We hypothesized that pelvic chemoradiotherapy (PCRT) given after systemic chemotherapy for metastatic bladder cancer (MTCC) might alter the pattern of disease recurrence, and reduce the complications and morbidity of intrapelvic disease relapse. A 74% locoregional relapse rate has been observed in MTCC patients with intrapelvic nodal disease after response to chemotherapy. To explore this hypothesis further, we performed a retrospective analysis and report the efficacy, toxicity and pattern of failure with this approach.*

Materials and methods: *Patients treated for MTCC who received consolidative PCRT following at least a partial response to systemic chemotherapy were identified and their charts reviewed for pelvic relapse, disease progression, survival, and toxicity.*

Results: *Twelve patients were identified and median follow-up was 15.6 months. Nine patients developed progressive disease and died, and median survival was 15.6 months. Three patients had pelvic progression (pelvic failure rate 25%). Median time to pelvic failure was 12.8 months. At last follow-up, three patients were alive and disease-free. No life-threatening toxicities were observed. The most common acute non-hematological toxicities were diarrhea and nausea.*

Conclusions: *These data support a hypothesis that consolidative PCRT following chemotherapy in MTCC patients with systemic disease control may be feasible and efficacious for improving pelvic disease control. This intervention should be considered for further study in prospective controlled clinical trials.*

Key Words: bladder neoplasms, radiotherapy, drug therapy, pelvic neoplasms

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Address correspondence to Dr. Eric Winquist, London Health Sciences Centre, 790 Commissioners Road East, London, Ontario N6A 4L6 Canada

Introduction

Metastatic transitional cell carcinoma of the bladder (MTCC) is chemosensitive with 50% of patients achieving objective response to first-line cisplatin-based combination chemotherapy such as methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) or gemcitabine plus cisplatin (GC).[1] Despite the relatively high response rate, the median survival time is 1 year.[1] Relapse may occur both locoregionally and distantly in lung, liver, bone and the central

nervous system.[1,2] Dimopoulos et al[2] have reported the pattern of failure in MTCC patients who responded to cisplatin-based chemotherapy, and observed that 74% of patients with nodal disease relapsed locoregionally. These authors speculated that consolidative surgery or radiotherapy might have value in these patients. Aggressive surgical resection of residual disease after a major response to chemotherapy may improve disease control and survival in selected patients with disease confined to the pelvis or lymph nodes.[3-5] However, radical surgery is not technically feasible for most patients, so typically patients achieving remission with chemotherapy are observed with the understanding that disease progression is inevitable and can occur both distantly and locoregionally.

MTCC is known to be radiosensitive, and radiotherapy may provide excellent palliation. Radical radiotherapy is also often offered to medically inoperable patients with muscle-invasive bladder cancer, or as a bladder-sparing alternative to radical cystectomy. The ability of radiotherapy to improve local pelvic control in these settings is enhanced by the concomitant administration of cisplatin, which functions as a radiosensitizer.[6] Consolidative postchemotherapy chemoradiotherapy has resulted in improved local control in other malignancies such as extensive small-cell lung cancer.[7] Several small, retrospective studies have investigated the role of postoperative adjuvant radiotherapy in advanced TCC of the upper urinary tract, and have both supported and refuted its benefit in local control and survival.[8-10]

Uncontrolled pelvic cancer is associated with manifold complications including pain, radiculopathy, obstructive uropathy, bowel obstruction and thrombosis. Although pelvic chemoradiotherapy (PCRT) might not be expected to influence the overall survival of patients with MTCC, it could reduce the rate of local progression and pelvic complications. Using this rationale, we have selectively offered consolidative PCRT with the intent of improving local control to patients presenting with MTCC and either an unresected primary bladder tumor or a component of pelvic recurrence. We report the results of these patients' pelvic failure rates, time to pelvic and disease progression, pattern of failure, overall survival, pelvic morbidity and toxicity of consolidative therapy.

Patients and methods

Eligible MTCC patients had either AJCC stage IV (T4b, N1-3 or M1)[11] with bladder primary *in situ* or recurrent disease with pelvic involvement, and had achieved at least a partial response to systemic chemotherapy. Patients included were seen at the London Regional Cancer Centre between January 1, 1996 and December 31, 2003. The study cohort consisted of those patients who also received consolidative pelvic radiotherapy with or without radiosensitizing chemotherapy with the intent of improving local control. Patients were excluded if radiotherapy was given solely for symptom relief. Patients with other active malignancies or who were inevaluable for response to chemotherapy were excluded.

Chemotherapy and radiation treatment were at the discretion of the treating physicians. Patients received chemotherapy until maximal response or unacceptable toxicity intervened. Response to treatment was based on imaging reports and/or clinical assessment, and was classified as either complete or partial. Complete response (CR) was defined as total disappearance of disease at all sites. As not all patients had measurable disease, partial response (PR) was defined as improvement of at least one disease site with no progression or new lesions identified at other sites. After completion of radiotherapy, patients were followed every 3 months with clinical examination and investigations including imaging.

The primary objectives were to determine the pelvic failure rate and the median time to pelvic failure. Secondary objectives were to determine the time to disease progression, overall survival time, pattern of first failure, pelvic morbidity and toxicity of consolidative treatment. Pelvic failure and disease progression was recorded at the date of first clinical or radiological identification. Progression-free status was censored to the date of the last clinical or radiological examination in which it was confirmed. Time to pelvic progression, time to disease progression, and overall survival were measured from the start date of systemic chemotherapy to the date of first pelvic progression, any progression or death, and death; respectively. Toxicity data for consolidative therapy was compiled using routine daily nursing assessment forms and physician progress notes and graded according to the National Cancer Institute common toxicity criteria scale (version 3.0).[12] Fisher's exact test was used to compare expected versus observed pelvic failures rates following consolidative radiotherapy. Survival curves were plotted using the Kaplan-Meier method.

Results

Patients

One hundred and one MTCC patients received systemic chemotherapy for either stage IV disease

TABLE 1. **Clinical information and outcomes**

Pt.	Clinical stage	Prior therapy	Disease sites	Chemo (cycles)	Resp.
1	T3aN3M1	None	Pelvic and distant nodes	GCi-28 (8)	PR
2	T4bN1M1	Intravesical	Pelvic wall and nodes, distant nodes	GCi-21 (8)	CR
3	Recurrent	Intravesical, cystectomy	Rectum	GCi-28 (4)	CR
4	T4aN0M1	None	Prostate, lung	GCa-21 (8)	PR
5	TXN1M1	None	Pelvic and distant nodes	GCi-28 (6)	PR
6	Recurrent	Cystectomy, pelvic RT	Pelvic nodes	MVAC (5)	PR
7	Recurrent	Cystectomy	Vaginal wall	MVAC (2)	PR
8	T4bN3M1	None	Seminal vesicle, pelvic wall, pelvic and distant nodes	MVAC (2)	PR
9	T4bN3M1	None	Pelvic wall, pelvic nodes, pelvic bone	GCi-21 (6)	PR
10	Recurrent	Cystectomy	Pelvic nodes	GCi-21 (5)	CR
11	Recurrent	Cystectomy	Pelvic and distant nodes and bone	GCi-28 (5)	PR
12	T4aN1M0	None	Seminal vesicles, pelvic nodes	MVAC (2)	PR

Abbreviations: RT, radiation; GCi, gemcitabine-cisplatin, GCa, gemcitabine-carboplatin; 21/28, day schedules; PR, partial progressive disease.
*Para-aortic nodes also radiated (patient 1: 45,25; patient 11: 33,11).

with an unresected primary bladder tumor or for relapse with a component of pelvic recurrence, and 34 had CR or PR. Twelve patients who received consolidative PCRT constitute the study population, Table 1. The median age was 72 years (range, 56 to 79) and four patients were female. Pelvic disease sites included: pelvic sidewall (three patients); seminal vesicle (two patients); and prostate, vagina, and rectum (one patient each). Seven patients had stage IV disease with an unresected bladder primary. Five patients had locoregional recurrence with or without distant metastases following radical cystectomy. Seven patients had distant disease involving bone (two patients), lung (one patient) and lymph nodes (five patients). Three patients had CR (25%) and nine had PR (75%) to systemic chemotherapy. Four patients received a median of two cycles of M-VAC (range, 2 to 5), all with PR. Eight patients received a median of six cycles of gemcitabine-cisplatin (range, 4 to 8) (3 CR and 5 PR). Five patients were treated on a 21-day schedule[13] (2 CR and 3 PR) and three on a 28-day schedule (1 CR and 2 PR). One patient with renal dysfunction achieved PR with gemcitabine and carboplatin on a 21-day schedule.[14]

Treatment

Pelvic radiotherapy was administered using megavoltage photons with four-field technique. Eleven patients received radiotherapy to a field that consisted of the pelvic tumor site(s) and pelvic lymph nodes at a median dose of 41.6 Gy in 23 daily fractions (range, 25 Gy/10 fractions to 45 Gy/25 fractions). One patient received radiation to the bladder only at a dose of 37.5 Gy in 15 fractions. In two patients, the radiation field included paraaortic lymph nodes (45 Gy/25 fractions and 33 Gy/11 fractions). Seven patients received a boost to the pelvic tumor at a median dose of 12.5 Gy in 5 fractions (range, 10 Gy/5 fractions to 17.5 Gy/7 fractions). Nine patients received concurrent chemotherapy with either cisplatin 20 mg/m^2 IV twice weekly (four patients; median of 9 doses; range, 4 to10) or carboplatin AUC 1.5 IV weekly (five patients; median of 3 doses; range, 3 to 4). Three patients did not receive concurrent chemotherapy due to concerns about increased radiation toxicity following gemcitabine-based systemic chemotherapy.

Pelvic failure rate and time to pelvic failure

Median follow-up was 15.6 months (range, 7.3 to 70.4).

RT (Gy dose, fraction)			Initial	Survival (mos.)		
Local	Locoregional		failure site	Disease-free	Overall	Status
55.8,31	45,25*	Ca	Liver	9.8	11.4	DOD
37.5,15	25,10	Ca	None	42.3	42.3	Alive, NED
45,25	45,25	Ca	Abdominal mesentery	7.2	9.4	DOD
50,20	32.5,13	Ca	Lung	10.0	11.6	DOD
37.5,15	0	Ca	Bladder	15.5	15.9	DOD
41.6,23	41.6,23	Ci	Vaginal wall	12.8	16.3	DOD
45,25	45,25	Ci	Brain	9.6	15.3	DOD
60.3,34	45,25	Ci	Bone	6.9	7.3	DOD
35,15	25,10	--	Pelvic bone and nodes	11.0	13.4	DOD
39.6,22	39.6,22	--	Brain	7.9	25.5	DOD
40,15	30,10*	--	None	52.8	52.8	Alive, NED
60,30	44,22	Ci	None	70.4	70.4	Alive, NED

response; CR, complete response; Ca, carboplatin; Ci, cisplatin; DOD, dead of disease; NED, no evidence of recurrent or

Three of twelve patients progressed in the pelvis, yielding a pelvic failure rate of 25%. This was significantly less than the nine patients expected based on observations by Dimopoulos et al[2] and assuming a similar risk in our population (p = 0.039, two-tailed Fisher's exact test). Median time to pelvic failure was 12.8 months (range, 11.0 to 15.5). The sites of pelvic first failure were the bladder, vaginal wall, and both pelvic nodes and bone, respectively, Table 2.

TABLE 2. **Pattern of First Failure***

Failure site	No. patients
Total no. patients	9
Pelvic only	3
Bladder	1
Vaginal wall	1
Pelvic bone	1
Pelvic nodes	1
Extrapelvic only	6
Liver	1
Lung	1
Brain	2
Bone	1
Abdominal mesentery	1

*Multiple failures possible

Time to disease progression, pattern of failure and overall survival

Nine patients experienced disease progression at any site, with a median progression time of 9.8

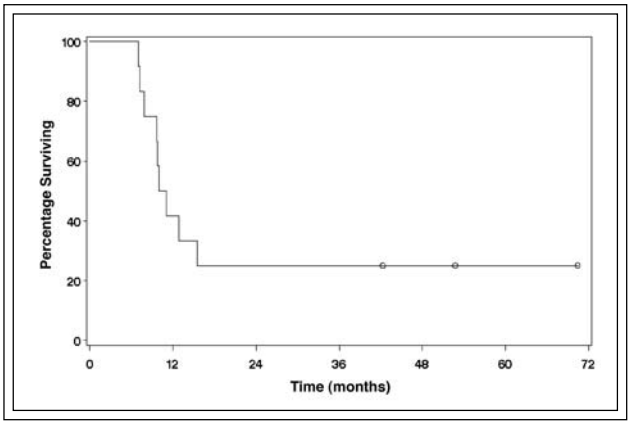

Figure 1. Progression-free survival. Circles indicate patients progression-free at last follow-up.

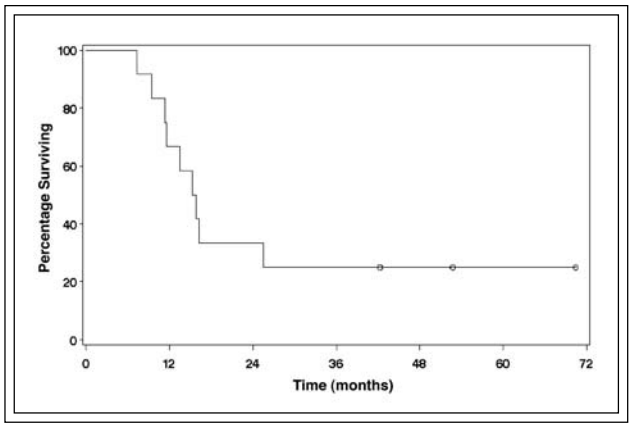

Figure 2. Overall survival. Circles indicate patients alive at last follow-up.

months (range, 6.9 to 15.5), Figure 1. Three patients were alive and disease-free at last follow-up, with a median disease-free survival of 52.8 months (range, 42.3 to 70.4). The most common site of initial progression outside the pelvis was the brain (two patients), with the other sites being liver, lung, bone and abdominal mesentery (one patient each), Table 2. Median overall survival was 15.6 months (95% CI, 11.6 to 25.5), with nine patients dying of progressive bladder cancer and three patients alive and censored to last follow-up, Figure 2.

Pelvic Morbidity

Pelvic complications were observed in all three patients experiencing pelvic progression. Most complications were of grade 3 severity (45%). Two patients had fatigue, anorexia, and pain. One patient experienced increased bone pain (grade 4) due to progression of bony and nodal lesions in the pelvis and was unable to walk. The second patient experienced grade 3 fatigue and developed a vaginorectal fistula with bleeding and pyuria as well as confusion secondary to infection. The third patient experienced progression in the bladder with chronic grade 3 hematuria and developed difficulty walking with grade 3 fatigue, weakness, dehydration, and ultimately died of obstructive renal failure.

Toxicity

Adverse events at least possibly related to consolidative therapy were recorded as worst grade by patient, Table 3. Events were classified as chronic if they occurred greater than 1 month after radiotherapy completion. Sensory neuropathies (e.g. paresthesia, ototoxicity) and complications present at an equal or greater severity at the start of consolidative therapy were not included. Five patients required treatment breaks from radiotherapy and six patients required breaks from concurrent chemotherapy. Two patients received a blood transfusion. There were no toxic deaths due to consolidative therapy. The most common non-hematological toxicities were diarrhea (eight patients) and nausea (seven patients), followed by constipation, dehydration, fatigue and rash (four patients each). Most adverse events were of mild to moderate severity (47% grade 1, 27% grade 2, 24% grade 3 and 2% grade 4). The most common severe toxicity was myelosuppression. Grade 3 fatigue and weakness were experienced by a patient with febrile neutropenia. One patient had recurrence of deep vein thrombosis during radiotherapy. A patient with grade 3 leg pain and leg edema began consolidative therapy with grade 2 pain and edema. Overall, baseline toxicity was present for 12 of the total 89 adverse events recorded. Seventeen percent of grade 2 adverse events were present at grade 1 severity at the start of consolidative therapy, while 33% of grade 3 toxicities were present at either grade 1 (57%) or grade 2 (43%) severity at baseline. One of the two grade 4 toxicities was present at grade 1 severity at baseline. Five patients experienced chronic complications following consolidative therapy. Listed by patient, these included: grade 2 enteritis and grade 1 suprapubic lymphedema; grade 2 bowel obstruction; grade 3 enteritis; grade 3 cystitis with chronic gross hematuria (likely due to bladder tumor progression); and grade 2 distal ureteric strictures requiring ongoing ureteric stenting.

Discussion

The prognosis of patients with MTCC remains grim. Even with modern chemotherapy, over 90% of patients die within 2 years.[1] Patients with only nodal or nonvisceral metastases have higher response and survival rates.[3,15] These patients also tend to recur in areas of prior disease following complete clinical response to systemic chemotherapy.[2,15,16] A prerequisite for long-term survival is the achievement of complete response to treatment. Based on these observations, several studies have investigated the role of surgical resection in such patients following chemotherapy.[3-5] Residual disease was found in 38% and 86% of patients with complete clinical response to chemotherapy, suggesting a need for consolidative therapy following even a major response to chemotherapy.[4,5] With the use of postchemotherapy surgery to verify complete response to chemotherapy

TABLE 3. **Acute toxicity related to consolidative therapy***

Toxicity	Grade (worst grade by patient)					Total
	1	2	3	4	5	
Non-hematologic						
Constitutional symptoms:						
Fatigue	2	1	1			4
Weight loss	1	1				2
Gastrointestinal:						
Anorexia	1	2				3
Diarrhea	7	1				8
Constipation	3	1				4
Dehydration	4					4
Nausea	4	3				7
Vomiting	3					3
Neurological:						
Abdominal pain	1	2				3
Pain, other	1	1	1			3
Muscle weakness			1			1
Renal/genitourinary:						
Hemoglobinuria	1					1
Urinary frequency/urgency	2	1				3
Vaginal bleeding	1					1
Other:						
Febrile neutropenia			1			1
Rash	2	2				4
Edema	2		1			3
Thrombus			1			1
Hematologic						
Leukocytopenia	1	2	4			7
Anemia	1	3				4
Thrombocytopenia	2	2	2			6
Neutropenia	1		3	1		5
Lymphopenia	2	2	6	1		11
Any toxicity	42	24	21	2	0	89
Total no. patients	11	9	7	2	0	**12**

*Multiple toxicities possible; includes toxicity data for RT with and without concurrent chemotherapy

or attain complete response following combined chemotherapy and surgery, 5-year survival was achieved in a third of patients.[4] Consolidative radiotherapy following GC chemotherapy has been prospectively studied in 20 patients with MTCC and was found to yield a 95% complete response rate with an enhanced disease free survival of 21 months and a low toxicity profile.[17]

Dimopoulos et al found that 74% of patients with nodal MTCC relapsed locoregionally following response to systemic chemotherapy.[2] In our study, all MTCC patients had a component of nodal pelvic disease and/or unresected primary cancer *in situ* prior to systemic chemotherapy and consolidative therapy and only 25% relapsed locoregionally. This suggests that consolidative PCRT may improve local disease control and result in fewer locoregional recurrences. The median time to pelvic failure, any failure, and death were 12.8 months, 9.8 months, and 15.6 months; respectively, consistent with published results for systemic chemotherapy alone. Notably, we observed three long-term survivors who have achieved median disease-free survivals of 42, 53 and 70 months. For all three patients, sites of residual disease following

chemotherapy were included in the radiation fields. Patients with pelvic progression in our study experienced serious complications including fistula formation, grade 4 pain, and death due to renal failure. Overall, and despite prior systemic chemotherapy, chemoradiotherapy was reasonably well tolerated with no life-threatening toxicities.

Our series is limited by its small sample size, lack of controls, heterogeneity of the chemotherapy and radiation used, and lack of quality of life data. Nevertheless, the low pelvic progression rate supports a hypothesis that consolidative PCRT following systemic chemotherapy may be of value for improving local disease control in selected patients without adding major toxicity. Although survival effects are likely to be minimal, patients could benefit from an improved quality of life by being spared pelvic disease progression and its associated morbidity. This benefit is predicated on minimal toxicities of PCRT outweighed by the benefits of enhanced pelvic tumor control. Surgical resection may be an alternative but is more invasive, and may not be suitable for all patients or feasible at all centers. For MTCC patients with pelvic disease in remission after systemic chemotherapy, benefits and costs of consolidative PCRT for pelvic disease control should be studied further in controlled clinical trials. □

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