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RESEARCH ARTICLE

Concurrent chemoradiotherapy with low dose weekly gemcitabine in medically inoperable muscle-invasive bladder cancer patients

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Abstract
Purpose We aimed to determine the efficacy and the toxicity of low dose weekly gemcitabine with radiation therapy in medically unfit muscle-invasive bladder cancer patients.
Methods Twenty-six patients were included into the retrospective analysis. Weekly gemcitabine was administered 75 mg/m^2 with a median dose of 63 Gy radiation therapy. Clinical target volume was defined as the urinary bladder only in conformal treatment planning.
Results Median follow-up was 51 months (range 14–118 months). Complete response rate was 62.5 %. The 5-year local progression-free survival, disease-specific survival and overall survival rates were 40.6, 59.5 and 58.5 %, respectively. Concurrent chemotherapy was continued in 80.7 % of patients without any interruption. Gemcitabine was stopped due to grade 3 thrombocytopenia ($n = 1$), cardiac angina ($n = 1$), chronic obstructive pulmonary disease exacerbation ($n = 1$) or patients' reluctance ($n = 2$).
Conclusions Low dose weekly gemcitabine with concurrent radiotherapy is a tolerable regimen and have comparable outcomes with platinum-based combined treatments in muscle-invasive bladder cancer. Prospective randomized trials can help in understanding the safety and efficacy of this treatment specially in medically unfit patients.

Keywords Bladder cancer · Concurrent gemcitabine · Medically unfit patients · Radiotherapy

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Introduction

Radical cystectomy with pelvic lymphadenectomy has been considered the standard treatment in muscle-invasive bladder cancer patients and 5-year overall survival rates are about 60 %.with this treatment [1] Alternatively, bladder-preserving strategies with maximal transurethral resection of bladder tumor followed by platinum-based chemoradiotherapy has been tested in randomized controlled trials [2–6]. In these studies, the complete response rates reported were 60–90 % and 5-year bladder intact survival rate was 40 % [2, 5, 6].

However, in medically inoperable patients, concomitant therapy may be more challenging due to the risk of enhanced toxicity. Unfortunately, in retrospective series single modality radiotherapy or chemotherapy failed to

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show any benefit regarding local control and survival [7–10]. Therefore, concurrent chemoradiotherapy with potentially less toxic radiosensitizing drugs may provide a better treatment option for future improvements in medically unfit patients. Gemcitabine, a potent radiosensitizing agent, may be a candidate for a combined integrated approach for this purpose. It has a synergistic effect with radiotherapy and can enhance local tumor eradication [11]. Favorable clinical response rates have been reported in locally advanced and metastatic transitional cell bladder carcinoma with gemcitabine [12]. Other investigators have also tested weekly gemcitabine combined with radiotherapy [13, 16]. They reported complete response rates of 88–100 % and bladder intact survival rate of 75–88 % at 20 months, respectively. Our center has also an experience with 75 mg/m^2 weekly gemcitabine, which revealed tolerability with radiotherapy in non-small cell lung and pancreatic cancer patients [17, 18].

In this study, we aimed to analyze the outcome of definitive radiotherapy with low dose weekly gemcitabine in muscle-invasive bladder cancer patients, who were medically unfit or refused to undergo surgery.

Methods

Patients' characteristics

The current study has been approved by Ethics Committee in our faculty. Patients treated between September 2000 and June 2009 in our center were included in this retrospective analysis. There were 26 patients with non-metastatic muscle-invasive bladder cancer who underwent chemoradiotherapy. All patients either were unfit for surgery due to comorbidities ($n = 24$) or refused to perform radical cystectomy ($n = 2$). Patient and tumor characteristics are shown in Table 1. Baseline Karnofsky performance status (KPS) scores were ≥60 for all patients. All patients were treated with transurethral resection (range 1–3 times) before their tumors progressed to muscle invasion. Previously, nine (34.6 %) patients had intravesical chemotherapy or BCG during the non-invasive stage of disease.

Cystoscopic evaluation with maximal transurethral resection was done prior to chemoradiotherapy. Computerized tomography and/or magnetic resonance imaging were used for intrapelvic and regional lymph nodes assessment. A metastatic work-up was performed for all patients.

Chemoradiotherapy

An 18 MV linear accelerator was used for the radiation therapy delivering a median total dose of 63 Gy (range 59.4–66.6 Gy) in 1.8 Gy/fraction. Three-field technique, single anterior and two lateral fields, was used in 3D-conformal treatment planning. Clinical target volume encompassed the urinary bladder with a 2 cm margin. It was aimed to cover 100 % of the treatment volume by the 95 % of the prescribed isodose with Dmax less than 107 %. Empty bladder was a mandatory condition for each fraction. Gemcitabine was given within 30 min of IV-infusion with 75 mg/m^2/week started on day 1 and planned to continue weekly until the last week of radiotherapy.

Physical examination, total blood counts, kidney function tests were done weekly and side effects were recorded once a week according to the common toxicity criteria (CTC) v2.0 [19]. Liver tests were obtained initially and at the end of chemoradiotherapy. Concurrent chemotherapy dose was reduced in patients, who experienced grade ≥3 toxicity.

Table 1 Patient and tumor characteristics

Characteristics	*n* (%)
Number of patients	26
Gender	
Male	24 (92.3 %)
Female	2 (7.7 %)
Age (years)	
Median	73
Range	49–89
Stage	
T2a-bN0M0	23 (88.4 %)
T3a-bN0M0	3 (11.6 %)
Tumor histology (carcinoma)	
Transitional cell	25 (96.1 %)
Squamous	1 (3.9 %)
Tumor grade	
Grade III	21 (80.7 %)
Grade II	1 (3.8 %)
Unknown	4 (15.3 %)

Evaluation and follow-up

The first cytoscopic and radiological evaluation was done 3 months after the end of chemoradiotherapy. Cystoscopy was performed every 4–6 months in the first 2 years, thereafter every 6 months for an additional 3 years and if clinically indicated. Radiological evaluation was done every 3 months for the first 2 years and thereafter every 6 months or if clinically indicated.

Statistical analyses

Local progression-free survival (LPFS) was measured from the date of chemoradiotherapy initiation to the date of local

progression. Disease-specific survival (DSS) was measured from the date of chemoradiotherapy initiation to date of death from bladder cancer. The overall survival (OS) was measured from the date of chemoradiotherapy initiation to the date of death from any cause. All survival curves were plotted using the Kaplan–Meier method.

Results

Toxicity analysis

All patients completed radiotherapy as planned and no treatment related death was observed. The median total dose of gemcitabine was 910 mg (range 130–1050 mg) and gemcitabine was administered in 21 (80.7 %) patients without any interruption. Chemotherapy was interrupted in an overall of five patients due to grade 3 thrombocytopenia ($n = 1$), cardiac angina ($n = 1$) and chronic obstructive pulmonary disease exacerbation ($n = 1$). Two patients received gemcitabine 1–3 weeks with radiotherapy and they refused to have chemotherapy thereafter.

Response and outcomes

No progression occurred during and at the end of chemoradiotherapy. Two patients were lost to follow-up. Fifteen (62.5 %) of 24 assessable patients achieved complete response. One of nine patients, who failed to achieve complete response was successfully salvaged by radical cystectomy. This patient had previously refused surgery and he died due to distant metastasis 25 months later. Other cases underwent systemic chemotherapy and/or transurethral resection. Salvage treatments in terms of tumor response were not successful in any of these patients. Seven of the patients died with local progression and one patient died due to liver metastasis. After the fourth time of superficial tumor excision, one patient is still alive without any local progression.

One of 15 patients, who initially responded to therapy died due to local failure. Consequently, the total failure rate was 41.6 %. Four cases in remission died with metastatic disease without any evidence of local disease. One patient had histologically proven secondary pancreatic cancer without evidence of bladder cancer recurrence at the time of death. Nine of 24 assessable patients are alive without any disease at the time of assessment.

Median follow-up was 51 months (range 14–118 months). The 5-year LPFS, DSS and OS were 40.6, 58.5 and 59.5 %, respectively. Survival curves are sketched in Fig. 1.

Discussion

Currently, platinum-based chemotherapy has been recommended for concomittant chemoradiation in locally advanced urinary bladder cancer as an alternative to radical cystectomy [2–6]. In RTOG 85-12 trial, cisplatin was administered with 64 Gy radiotherapy in 42 patients and 4-year survival rates were 64 % in T2, 24 % in T3–T4 patients with a 66 % complete response rate [5]. Concurrent weekly gemcitabine with radiotherapy has been tested

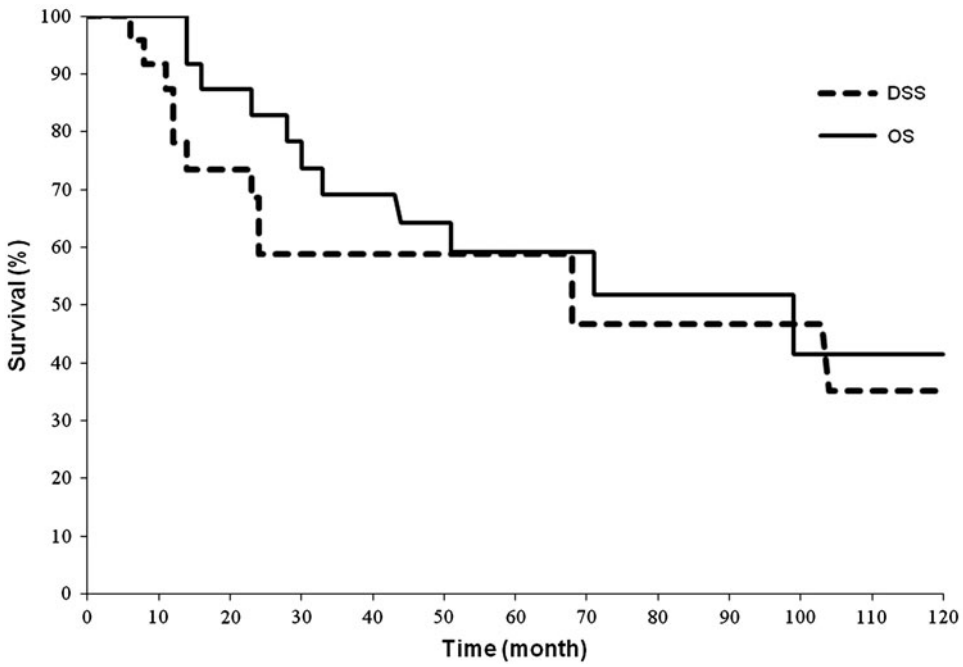

Fig. 1 Kaplan–Meier projections of survival curves

Table 2 Survival and toxicity results of concurrent gemcitabine-based chemoradiotherapy studies

Study	Radiotherapy	Gemcitabine	Median follow-up	Survival	Acute toxicity (grade 2–5)		
					Hematological	Genitourinary	Intestinal
Caffo et al. [13] ($n = 16$)	36 Gy to small pelvis, 54 Gy to bladder	MTD 400 mg/m^2/once weekly × 6 weeks[a]	19 months	5 years OS 70.1 % DSS 78.9 %	Grade 3 neutropenia 12.5 %	NA	Grade 4 6.2 % Grade 5 6.2 %
Oh et al. [15] ($n = 24$)	60 Gy to bladder	27 mg/m^2/twice weekly × 6 weeks	5.6 years	5 years OS 76 % DFS 82 %	NA	NA	NA
Borut and Lijana [16] ($n = 20$)	46–50 Gy to bladder + obturator lymphatic, 60 Gy to bladder	75 mg/m^2/weekly × 6 weeks	26 months	3 years PFS 82 %	Grade 2 20 % Grade 5 %	Grade 2 40 % Grade 3 10 %	Grade 2 50 % Grade 3 5 %
Our results ($n = 26$)	63 Gy to bladder	75 mg/m^2/weekly × 6 weeks	51 months	5 years OS 59.5 % DSS 58.5 % LPFS 40.6 %	Grade 3 thrombocytopenia 3.8 %	Grade 2 19.3 % Grade 3 none	Grade 2 19.5 % Grade 3 none

NA not applicable, *MTD* maximally tolerated dose, *OS* overall survival, *DFS* disease-free survival, *DSS* disease-specific survival, *LPFS* local progression-free survival

[a] Cisplatin: 100 mg/m^2/21d × 2

in phase I studies [13–16]. In these studies, gemcitabine was administered in different dose schedules either with cisplatin or alone (Table 2).

Either gemcitabine- or cisplatin-based concurrent chemoradiotherapy studies are shown in Table 3. Caffo et al. [13] administered cisplatin 100 mg/m^2/days 1 and 21 with weekly gemcitabine 400 mg/m^2. Radiotherapy dose was 54 Gy in this study. Other authors tested concurrent gemcitabine 27 mg/m^2/twice weekly with 60 Gy radiotherapy or 150 mg/m^2/week with 52.5 Gy radiotherapy [14, 15]. In these studies, 5-year overall survival and disease-free survival rates were 76 and 82 %, respectively [15]. Authors observed a 57 % failure rate in stage T2/T3 and cystectomy eligible patients. Borut and Lijana [16] reported an acceptable result with weekly 75 mg/m^2 gemcitabine as regards toxicity and response in a phase I study. In this study, the 3-year disease-free survival was 81 %. In all these studies, gemcitabine was administered in low doses for the purpose of radiosensitization. Gemcitabine increases toxicity when administered with definitive radiotherapy. Meanwhile, low doses may help reduction of chemotherapy side effects during concurrent treatment. Consequently, our results showed that both survival and local control rates, and toxicity are comparable with the previous studies [13–16]. In our study, concomittant gemcitabine was administered in 81 % of patients without any omission due to toxicity. There was not any grade 3 intestinal or genitourinary side effects observed and we did not observe any radiotherapy interruption due to toxicity. The 3D-conformal RT technique availability and small treatment volumes encompassing only the urinary bladder provided a chance for dose escalation without any severe toxicity. Moreover, the prevailing side effect for gemcitabine (thrombocytopenia: grade 3, 4 %) was reasonable.

Table 3 Gemcitabine-based and cisplatin-based concurrent chemoradiotherapy studies

Study	*n*	Concurrent treatment	5-year OS (%)
Kaufman et al. [2]	34	64 Gy RT with cisplatin and 5-fluorouracil	83 (3 years)
Shipley et al. [3]	123	64.8 Gy RT with cisplatin	48
Tester et al. [5]	42	64 Gy RT with cisplatin	52
Caffo et al. [13]	16	54 Gy RT with cisplatin and gemcitabine	70.1
Oh et al. [15]	24	60 Gy RT with gemcitabine	76
Borut and Lijana [16]	20	60 Gy RT with gemcitabine	82 (PFS)
Our study[a]	26	63 Gy RT with gemcitabine	59.5

OS overall survival, *PFS* progression-free survival

[a] All patients are medically unfit to surgery

In conclusion, although the platinum-based concurrent treatments are recommended in the literature, we showed that low dose weekly gemcitabine with radiotherapy can also be an option in medically unfit urinary bladder cancer patients. Prospective randomized trials are required defining the safety and efficacy of this protocol in bladder preserving strategies.

Conflict of interest None declared.

References

1. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1.054 patients. J Clin Oncol. 2001;19:666–75.
2. Kaufman DS, Winter KA, Shipley WU, Heney NM, Chetner MP, Souhami L, et al. The initial results in muscle-invading bladder cancer of RTOG 95–06: phase I/II trial of transurethral surgery plus radiation therapy by selective bladder preservation or cystectomy depending on the initial response. Oncologist. 2000;5:471–6.
3. Shipley WU, Winter KA, Kaufman DS, Lee WR, Heney NM, Tester WR, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89–03. J Clin Oncol. 1998;16:3576–83.
4. Tester W, Caplan R, Heaney J, Venner P, Whittington R, Byhardt R, et al. Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: Results of Radiation Oncology Group phase II trial 88–02. J Clin Oncol. 1996;14:119–26.
5. Tester W, Porter A, Asbell S, Coughlin C, Haeney J, Krall J, et al. Combined modality program with possible organ preservation for invasive bladder carcinoma: results of RTOG protocol 85–12. Int J Radiat Oncol Biol Phys. 1993;25:783–90.
6. Shipley WU, Kaufman DS, Zehr E, Heney NM, Lane SC, Thakral HK, et al. Selective bladder preservation by combined modality protocol treatment. Long-term outcomes of 190 patients with invasive bladder cancer. Urology. 2002;60:62–8.
7. Shelley MD, Barber J, Wilt T, Mason MD. Surgery versus radiotherapy for muscle invasive bladder cancer. Cochrane Database Syst Rev. 2002;1:CD002079.
8. Quilty PM, Duncan W. Primary radical radiotherapy for T3 transitional cell cancer of the bladder: an analysis of survival and control. Int J Radiat Oncol Biol Phys. 1986;12:853–60.
9. Goffinet DR, Schneider MJ, Glatstein EJ, Ludwig H, Ray GR, Dunnick NR, et al. Bladder cancer: results of radiation therapy in 384 patients. Radiology. 1975;117:149–53.
10. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet. 2003;361:1927–34.
11. Wilson DG, Bentzen SM, Harari PM. Biologic basis for combining drugs with radiation. Sem Radiat Oncol. 2006;16:2–9.
12. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000;17:3068–77.
13. Caffo O, Fellin G, Graffer U, Valduga F, Bolner A, Luciani L, et al. Phase I study of gemcitabine and radiotherapy plus cisplatin after transurethral resection as conservative treatment for infiltrating bladder cancer. Int J Radiat Oncol Biol Phys. 2003;57:1310–6.
14. Sangar VK, McBain CA, Lyons J, Ramani VA, Logue JP, Wylie JP, et al. Phase I study of conformal radiotherapy with concurrent gemcitabine in locally advanced bladder cancer. Int J Radiat Oncol Biol Phys. 2005;61:420–5.
15. Oh KS, Soto DE, Smith DC, Montie JE, Lee CT, Sandler HM. Combined modality therapy with gemcitabine and radiation therapy as a bladder preservation strategy: long term results of a phase I trial. Int J Radiat Oncol Biol Phys. 2009;74:511–7.
16. Borut K, Lijana ZK. Phase I study of radiochemotherapy with gemcitabine in invasive bladder cancer. Radiother Oncol. 2012;102:412–5.
17. Abacioglu U, Yumuk PF, Caglar H, Sengoz M, Turhal NS. Concurrent chemoradiotherapy with low dose weekly gemcitabine in stage III non small cell lung cancer. BMC Cancer. 2005;5:71.
18. Atasoy BM, Dane F, Ucuncu Kefeli A, Caglar H, Cingi A, Turhal NS, et al. Concomitant chemoradiotherapy with low dose weekly gemcitabine for non-metastatic unresectable pancreatic cancer. Turk J Gastroenterol. 2011;22:60–4.
19. Cancer Therapy Evaluation Program (1999) Common Toxicity Criteria, Version 2.0.http://www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf. Accessed 20 Jan 2011.