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Original article

Concurrent chemoradiotherapy in elderly patients with muscle-invasive bladder cancer: A single-center experience

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ABSTRACT

Background: Bladder cancer is a disease frequently seen in the elderly. Frail and elderly patients with muscle-invasive bladder cancer (MIBC) are often unfit for surgery. While concurrent chemoradiotherapy (CCRT) is a well-established alternative treatment modality, only a small proportion of elderly patients receive CCRT. The purpose of this article is to review our experience with CCRT in elderly MIBC patients.
Methods: Between January 1, 2007 and December 31, 2013, we retrospectively reviewed patients aged >75 who were treated with CCRT at Taipei Veterans General Hospital. Patients' characteristics, therapeutic strategy, clinical outcomes, and treatment-related toxicities were assessed.
Results: Nineteen patients (4 females and 15 males) were identified. The median age was 79.5 years (range, 78.5–84.0 years) and the median follow-up was 33.7 months (interquartile range, 19.1–51.8 months). The major adverse event was grade 3 or grade 4 neutropenia, which developed in 10 of the 19 patients. No treatment-related mortality occurred. We found no association between prognosis and the chemotherapy regimen. Chemotherapy with a conventional dose of gemcitabine (800–1000 mg/m^2) was well tolerated. The two-year and three-year estimated overall survival rates were 74% and 60%, respectively.
Conclusion: CCRT after complete transurethral resection of the bladder tumor is feasible for elderly patients with MIBC. The conventional dose of gemcitabine as a chemosensitizer is adequate in the elderly population, but further investigation is needed.

1. Introduction

Bladder cancer is one of the most common cancers in the world. It is estimated that around 74,000 new cases of bladder cancer and 16,000 bladder cancer-related deaths will occur in the United States in 2015.[1] It is prominent in men and in the elderly population. In Taiwan, 2199 new cases of bladder cancer were reported in 2011. The median age at diagnosis was 71 years.[2]

Radical cystectomy with pelvic lymph node dissection is the standard treatment for muscle-invasive bladder cancer (MIBC).[3] Bladder-preserving approaches, including transurethral resection of the bladder tumor (TURBT) followed by chemotherapy, radiotherapy, or a combination of chemotherapy and radiotherapy are alternatively strategies for patients unfit for radical cystectomy or for elderly patients with increased risks of morbidity or mortality. Radiotherapy is commonly used to treat MIBC, but radiotherapy alone is inferior to radical cystectomy and combinations of concurrent radiosensitizing chemotherapy.[4–6] Although concurrent chemoradiotherapy (CCRT) provides a survival benefit and allows bladder preservation, CCRT in the elderly population is usually underused.[7,8] In Taiwan, only 6–7% of MIBC patients aged >70 received CCRT.[2] In addition, the use of gemcitabine as radiosensitizing agent is rarely discussed.[9–11]

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We hereby present our clinical experience with elderly MIBC patients treated with CCRT.

2. Patients and methods

2.1. Patients

We reviewed the medical records of consecutive adult patients with bladder cancer who were referrals from primary or secondary health professionals or newly diagnosed at Taipei Veterans General Hospital between January 2007 and December 2013. All cases were pathologically confirmed. The inclusion criteria included age >75 years, pathological diagnosis of urothelial carcinoma, newly diagnosed muscle-invasive bladder cancer, and patients receiving CCRT after complete TURBT. Patients with prior non-MIBC or MIBC with distant metastasis were excluded. Patients' clinical information, including therapeutic strategies, toxicities and comorbidities, was collected, and patients were followed until either death, loss of follow-up or January 31, 2015.

2.2. Concurrent chemoradiotherapy

Either chemotherapy or radiotherapy was started within three months of complete TURBT. Radiotherapy doses of 40–45 Gy were used to treat the whole bladder and in some instances the pelvic lymph nodes. Some patients also received a sequential boost to the tumor bed for a total dose of 55–65 Gy. Chemotherapy was administered concurrently with radiotherapy or in the peri-radiotherapy period. Patients treated with sequential radiotherapy after neoadjuvant chemotherapy were excluded from this study.

2.3. Outcomes and statistical analysis

Descriptive statistics were used to describe the patients' characteristics, disease stages and treatment features, as well as treatment-associated toxicities. Overall survival (OS) and progression-free survival (PFS) were illustrated by means of the Kaplan–Meier estimate. Progression was defined as development of distant metastasis or local recurrence of a bladder tumor. PFS was calculated from the date of TURBT to the date of the first cystoscopic finding or radiographic evidence of disease progression, death, or the last follow-up visit. Survival was calculated from the date of TURBT to the date of death or the last follow-up visit. All analysis was performed using IBM SPSS Statistics (version 21) and conducted in February 2015.

3. Results

3.1. Patient characteristics

Between January 1, 2007 and December 31, 2013, we identified 44 patients receiving CCRT from a total of 933 patients with newly diagnosed bladder cancer. Of these 44 CCRT patients, 19 patients, including four women and 15 men, were aged over 75 and were diagnosed with MIBC. Their median age was 79.5 years (interquartile range, 78.5–84.0 years).

All enrolled patients had MIBC with or without nodal metastasis and were treated with complete TURBT and adjuvant CCRT. All patients' ECOG performance status was between 0 and 1. Clinical staging revealed that 14 patients were T2N0, two were T2N1, one was T4N0 and one was T4N3. Eleven patients received gemcitabine (800–1000 mg/m^2, given on days 1 and 8 and repeated every 21 days) combined with cisplatin (day 1, repeated every 21 days) or carboplatin (day 1, repeated every 21 days), 4 patients used CMV (cisplatin, methotrexate and vinblastin), three patients used weekly carboplatin, and one patient took oral tegafur plus uracil daily for three years. Eight patients used carboplatin-based chemotherapy because of impaired renal function. Patients' characteristics are summarized in Table 1.

3.2. Toxicity

Ten of the 19 patients developed grade 3 or grade 4 neutropenia, but only one patient had febrile neutropenia and needed hospitalization. Chemotherapy with gemcitabine showed no associated risk of neutropenia. Four patients had grade 1 or grade 2 renal toxicity, and two patients experienced grade 3 hepatic toxicity. Both renal and hepatic injuries resolved completely after adjusting or discontinuing chemotherapy. No treatment-related mortality was observed in this study (Table 2).

Radiation-associated cystitis developed in one patient. Two patients experienced radiation colitis and one was hospitalized. Radiation-associated dermatitis was noted in one patient. One patient withdrew from chemotherapy after two cycles but completed radiotherapy. Furthermore, reactivation of hepatitis B happened in one patient and subsided after treatment with entecavir and termination of chemotherapy.

3.3. Overall survival and PFS

Overall, the median follow-up was 33.7 months (interquartile range, 19.1–51.8 months) and the PFS was 27.9 months (interquartile range, 14.5–44.2 months) (Fig. 1). At the time of analysis, 5 patients had progressed, including 2 patients with local recurrence and 3 patients with distant metastasis. Six patients died — five from disease progression and one from ischemic bowel disease. The two-year and three-year overall survival rates were 74% and 60%, respectively. We found no significant association between prognosis and chemotherapy regimens.

Table 1
Patient characteristics.

Variable	N (%), median (range)
Gender	
M	15 (78.9)
F	4 (21.1)
Age	79.5 (78.5–84.0)
Stage	
T2N0	14 (73.6)
T2N1	2 (10.5)
T4N0	1 (5.2)
T4N3	1 (5.2)
Chemotherapy	
GC	11 (57.9)
CMV	4 (21.1)
Others	4 (21.1)
Carboplatin base	8 (42.1)
AUC	4–6
Cisplatin base	10 (52.6)
Dose	35 (30–40) mg/m^2
Radiation	
Bladder ± Plevis	45 Gy (45–46)
Tumor	58.6 Gy (54–62.8)
Estimated GFR	42.3 (26.0–59.8) ml/min
Obstructive uropathy	6 (30.0)
Comorbidity	
DM	9 (47.4)
HTN	12 (63.2)
CKD	9 (47.4)
CHF	2 (10.5)
COPD	3 (15.8)
CVA	4 (21.1)
CAD	8 (42.1)