Efficacy of long-term extended nursing services combined with atezolizumab in patients with bladder cancer after endoscopic bladder resection

Yao Song, BD; Pengjuan Ren, BD; Yang Wu, BD; Baodi Zhang, BD; Junrong Wang, BD; Yue Li, BD*

Abstract

Background: Nursing has been reported to effectively ameliorate physical movement, significantly decrease postoperative complications, and markedly improve the quality of life in patients with bladder cancer after endoscopic bladder resection. Atezolizumab (ATZ) has been approved as effective therapy for patients with bladder cancer. This study was aimed to assess the efficacy of long-term extended nursing services combined with ATZ in patients with bladder cancer after endoscopic bladder resection.

Methods: A total of one 126 patients diagnosed with bladder cancer underwent endoscopic bladder resection were recruited in this study. Patients were randomly allocated into the long-term conventional nursing plus atezolizumab (LTCN-ATZ) (n = 60) and long-term extended nursing services plus atezolizumab (LTENS-ATZ) groups (n = 66). The renal function, physical movement, postoperative complications, the quality of life, survival, and recurrence were examined in patients in LTCN-ATZ and LTENS-ATZ groups during 36-month follow up.

Results: Data in the current study demonstrated that the renal function, quality of life, satisfaction anxiety and depression for LTENS-ATZ group was significantly improved compared with that of LTCN-ATZ group. The occurrence rate was significantly lower, and the length of hospital stay was shorter for LTENS-ATZ than that of LTCN-ATZ group. Outcomes demonstrated that LTENS-ATZ increased survival and decreased the occurrence compared to those patients in LTENS-ATZ group.

Conclusion: In conclusion, outcomes in this study indicate that LTENS-ATZ improves renal function, and quality of life and prognosis in patients with bladder cancer after endoscopic bladder resection.

Abbreviations: ATZ = atezolizumab, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate, LTCN-ATZ = long-term conventional nursing plus atezolizumab, LTENS-ATZ = long-term extended nursing services plus atezolizumab, PD-L1 = programmed death ligand 1, TRAEs = treatment-related adverse events.

Keywords: atezolizumab, bladder cancer, long-term extended nursing services, quality of life, renal function

1. Introduction

Bladder cancer is one of the most common malignancies in the urinary system worldwide. Risk factors for bladder cancer include race, age, sex, diabetes, smoking, and genetic factors. Currently, endoscopic bladder resection has been widely applied for the treatment of patients with bladder cancer. Patients diagnosed with bladder cancer are typically older and have a high risk of renal function impairment. Most bladder cancer patients still require post chemotherapy treatment after the endoscopic bladder resection to eliminate residual tumor cells, which further improves survival and prognosis of bladder cancer patients. However, endoscopic bladder resection is associated with high risks of perioperative and long-term morbidity and mortality, including subsequent decline in renal function and occurrence.

Clinically, evidences found that nursing acts as adjuvant therapy to improve quality of life and postoperative syndrome for bladder cancer patients after surgery and intravesical chemotherapy. Li et al reported that extended nursing service optimizes the nursing mode that improves quality of life scores and prognosis of patients with bladder cancer after undergoing...
endoscopic bladder resection. In addition, C Paterson et al indicated that supportive care is needed for patients with muscle invasive bladder cancer to manage the disease and decrease complications. Nonsurgical care for bladder cancer patients is associated with increasing patient travel distance and decreased all-cause and bladder-cancer specific mortality. Furthermore, nursing services cooperated with effective treatment can significantly improve the confidence of patients, enhance compliance and improve the living status of patients. Hence, it is crucial to emphasize the importance of long-term extended nursing services for patients with bladder cancer after surgery.

Programmed death ligand 1 (PD-L1), an immune checkpoint, can bind to programmed death-1 (PD-1) or B7-1, which further regulates T cell function and activate T lymphocytes and other immune cells. Atezolizumab (ATZ) is one of Anti-PD-L1 antibodies and is an FcR binding-deficient that is widely used for the treatment of clinical cancer patients. Currently, ATZ have shown a significantly anti-cancer activity and manageable safety profile for cancer patients, which has been approved as second-line therapy for advanced bladder cancer. Notably, ATZ reduces immunosuppressive signals found within the tumor microenvironment and increases T-cell-mediated immunity against the tumor cells. It demonstrates a correlation between preoperative renal insufficiency and worse prognosis, underscoring the importance of renal function in the treatment of patients with bladder cancer after surgery. Combining radiation therapy and ATZ is expected to induce a synergistic abscopal effect, which can cause tumor regression at not only the irradiated field but also out of the irradiated field. Neoadjuvant gemcitabine and cisplatin plus ATZ are a promising regimen for muscle-invasive bladder cancer, which improve survival and prognosis of clinical patients. Although the role extended nursing service in improving the long-term prognosis of patients with bladder cancer after undergoing endoscopic bladder endoscopic resection, its efficacy on renal function has not investigated. In addition, immunotherapy of ATZ offers an alternative treatment for patients with bladder cancer, which improves survival of clinical patients.

In this study, we systematically evaluated the efficacy of long-term extended nursing services (LTENS) combined with ATZ (LTENS-ATZ) in bladder cancer patients after endoscopic bladder resection. The effects of LTENS-ATZ on improvement of renal function, physical movement, postoperative complications, the quality of life, survival, and recurrence in bladder cancer patients after endoscopic resection.

2. Materials and Methods

2.1. Study participants

A total 126 patients with bladder cancer after endoscopic bladder resection in the first branch of Hongqi Hospital Affiliated to Mudanjiang Medical University (Mudanjiang, China) were enrolled into the study between May 2015 and June 2018. This study was reviewed and approved by the human investigational review board of the first branch of Hongqi Hospital Affiliated (IRB: 2015005012A01). All patients gave their written informed consent. All methods were carried out in accordance with the clinical guidelines of the first branch of Hongqi Hospital Affiliated to Mudanjiang Medical University. Enrollment was restricted to PD-L1-selected patients (tumor-infiltrating immune cell 2/3 (IC1/2/3) status and PD-L1 expression on IC of ≥1% per VENTANA SP142 PD-L1 immunohistochemistry assay. Exclusion criteria were as follows: patients with cancer history; patients with serious other diseases, such as chronic renal failure, congenital heart disease, and liver diseases; the estimated survival time less than 12 months; pregnant women; recurrent bladder cancer; renal transplant; patients with infectious diseases.

2.2. Nursing method

All bladder cancer patients received ATZ treatment after endoscopic bladder resection. Patients were received intravenous infusion of 1200 mg of ATZ treatment after RECIST v1.1 criteria. Postoperative patients in the control group received the long-term conventional nursing including the introductions of disease characteristics, postoperative vital signs assessment, possible complications record and medication reminder. Patients in the long-term extended nursing services group received the conventional nursing and additional extended nursing service. Extended nursing services include sufficient communications with patients, regular telephone follow-up after leaving hospital, daily medication reminder, operative countermeasures, regular visit, and outpatient reviews. One doctor and three nurses allocated to every six patients. Patient clinical data were collected at baseline and follow up.

2.3. Outcomes measurement

Anxiety, depression, and health-related quality of life of patients in two groups were measured using SAS, SDS, and SF-36 scores, respectively. The estimated glomerular filtration rate (eGFR) was repeated every 6 months, along with repeat assessment of symptom burden by the MSAS-SF. Treatment-related adverse events (TRAEs) were graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 3.0. Overall survival and occurrence were defined from the time from nursing in hospital after surgery the last follow-up. Serum creatinine in clinical patients was measured using the Jaffe method on a Beckman DxC800 general chemistry analyzer (Beckman Coulter, Inc.). The eGFR was calculated by the modification of diet in renal disease or Nankivell methods.

2.4. Statistical analysis

Clinical data was expressed by mean ± standard deviation (SD) or n (%). Data are analyzed by using statistical software SPSS 23.0 (Chicago, IL). A t or χ² test was adopted for comparisons between groups. Survival and occurrence were analyzed by Kaplan–Meier method. P < .05 was established to be a difference of statistical significance.

3. Results

3.1. The baseline characteristics of bladder cancer patients

Bladder cancer patients after endoscopic bladder resection randomly received LTNC (n = 60) or LTENS (n = 66). The baseline characteristics of bladder cancer patients are shown in Table 1. There was no statistically significant difference in the clinical baseline characteristics including race, sex, tumor stage, baseline renal function, tumor grade, PD-L1 status, and site of primary tumor between LTENS-ATZ and LTNC-ATZ group (P > .05). The Flow chart for patients with patients with bladder cancer after endoscopic bladder resection was shown in Figure 1.

3.2. The comparison of length of hospital stays, postoperative complications, and satisfaction between LTENS-ATZ and LTNC-ATZ group

Outcomes demonstrated that length of hospital stay of bladder cancer patients after endoscopic bladder resection in LTENS-ATZ group was shorter than that in LTNC-ATZ group.
LTENS decreased the occurrence rate of postoperative complications and increased satisfaction compared with the LTNC-ATZ group ($P < .05$, Table 2).

### 3.3. The comparison of anxiety, depression, and health-related quality of life scores between LTENS-ATZ and LTNC-ATZ group

Anxiety, depression and health-related quality of life scores of bladder cancer patients after endoscopic bladder resection were compared between LTENS-ATZ and LTNC-ATZ group. Data showed that SAS, SDS and SF-36 scores of bladder cancer patients in LTENS-ATZ were lower than that in LTNC-ATZ group ($P < .05$, Table 3).

### 3.4. The comparison of investigator-assessed response rates between LTENS-ATZ and LTNC-ATZ group

Data analysis showed that LTENS increased RECIST v1.1 response rate for bladder cancer patients after endoscopic bladder resection compared with LTNC. As shown in Table 4, the response rate was 50.0% in for patients in LTENS-ATZ group, which was higher than patients in LTNC-ATZ group (35.0%).

### 3.5. The comparison of TRAEs between LTENS-ATZ and LTNC-ATZ group

During ATZ treatment, TRAEs were recorded for patients after endoscopic bladder resection. As shown in Table 5, the most common treatment-related adverse events in two groups were fatigue, rash, pyrexia, arthralgia, decreased appetite, nausea, diarrhea, and pruritus. LTENS decreased treatment-related adverse events compared to LTNC ($P < .05$). Data analyses revealed that 36% of patients and 58% percent of patients had TRAEs of any grade in LTENS-ATZ and LTNC-ATZ group, respectively. A total of 6% of patients and 15% of patients presented a grade 3 to 4 related adverse events in LTENS-ATZ and LTNC-ATZ group, respectively.

### Table 1

| Groups    | LTNC-ATZ  | LTENS-ATZ |
|-----------|-----------|-----------|
| Number    | 60 (47.6%)| 66 (52.4%)|
| Age (yr)  | 58.2 ± 10.5| 58.6 ± 9.8|
| Gender    |           |           |
| Male      | 32 (25.4%)| 34 (27.0%)|
| Female    | 28 (22.2%)| 32 (25.4%)|
| Race      |           |           |
| Han Chinese | 46 (36.5%)| 50 (39.7%)|
| The Korean nationality | 14 (11.1%)| 16 (12.7%)|
| BMI Index (kg/m²) | 22.1 ± 2.4| 22.4 ± 2.2|
| Site of primary tumor, n (%) |           |           |
| Bladder   | 60 (47.6%)| 66 (52.4%)|
| Renal function |           |           |
| sCr (mg/dL) | 3.0 ± 0.5  | 3.1 ± 0.5  |
| BUN (mg/dL) | 23.6 ± 4.0 | 23.2 ± 4.2 |
| Alb (mg/mL) | 22.0 ± 4.5 | 22.7 ± 5.2 |
| eGFR (mL/min/1.73m²) | 50.4 ± 8.3 | 50.0 ± 8.6 |
| Tumor grade |           |           |
| Low grade | 35 (58.3%)| 39 (59.1%)|
| High grade | 25 (41.7%)| 27 (40.9%)|
| Tumor stage |           |           |
| 1A        | 35 (27.8%)| 39 (31.0%)|
| 1C        | 25 (19.8%)| 27 (21.4%)|
| PD-L1 status |           |           |
| PD-L1 IC1 | 15 (25.0%)| 20 (30.3%)|
| PD-L1 IC2/3 | 45 (75.0%)| 46 (69.7%)|
| Tumor size (cm) |           |           |
| ≤2.5      | 48 (80.0%)| 50 (75.8%)|
| >2.5      | 12 (20.0%)| 16 (14.2%)|

Data are shown as mean ± SD or number (%). Percent PD-L1 expression on IC per central evaluation using the VENTANA SP142 immunohistochemistry assay. Alb = albumin, BMI = body mass index, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate, LTENS-ATZ = long-term extended nursing services plus atezolizumab, LTNC-ATZ = long-term conventional nursing plus atezolizumab, PD-L1 = programmed death ligand 1, sCr = serum creatinine.
### Table 2
The comparison of the length of hospital stay, postoperative complications, and satisfaction between LTENS-ATZ and LTNC-ATZ group.

| Groups          | LTNC-ATZ | LTENS-ATZ | P value |
|-----------------|----------|-----------|---------|
| Length of hospital stay (d) | 13.5 ± 3.5 | 8.5 ± 1.5 | .038    |
| Postoperative complications | 10 (16.7%)  | 2 (3.0%)  | .015    |
| Infection       | 3 (5.0%)  | 1 (1.5%)  | .040    |
| Hemorrhage      | 4 (6.7%)  | 1 (1.5%)  | .036    |
| Bedore          | 2 (3.3%)  | 1 (1.5%)  | .049    |
| Malnutrition    | 1 (2.0%)  | 1 (1.5%)  | .040    |
| The occurrence rate of complications | 12 (20.0%) | 4 (6.1%)  | .017    |
| Unsatisfied     | 15 (25.0%) | 4 (6.1%)  | .010    |
| Satisfied       | 35 (56.3%) | 21 (31.8%) | .025    |
| Very satisfied  | 10 (16.7%) | 41 (62.1%) | .002    |
| Degree of satisfaction | 45 (73.3%) | 62 (93.9%) | .026    |

LTENS-ATZ = long-term extended nursing services plus atezolizumab, LTNC-ATZ = long-term conventional nursing plus atezolizumab

### Table 3
The comparison of the length of hospital stay, postoperative complications, and satisfaction between LTENS-ATZ and LTNC-ATZ group.

| Groups          | LTNC-ATZ | LTENS-ATZ | P value |
|-----------------|----------|-----------|---------|
| SAS             | 34.5 ± 5.0 | 22.2 ± 4.8 | .022    |
| SDS             | 38.3 ± 4.6 | 23.8 ± 4.2 | .012    |
| SF-36           | 70.2 ± 5.8 | 86.4 ± 7.5 | .033    |

LTENS-ATZ = long-term extended nursing services plus atezolizumab, LTNC-ATZ = long-term conventional nursing plus atezolizumab, SAS = Self-Rating Anxiety Scale, SDS = Self-Rating Depression Scale, SF-36 = 36 health survey questionnaire.

### Table 4
The comparison of the length of hospital stay, postoperative complications, and satisfaction between LTENS-ATZ and LTNC-ATZ group.

| Groups          | LTNC-ATZ | LTENS-ATZ | P value |
|-----------------|----------|-----------|---------|
| REGIST version 1.1 criteria by independent review |              |
| ORR, n (%) (95% CI) | 21 (33) (29, 40) | 33 (50) (40, 60) | .038    |
| CR, n (%)       | 8 (13)   | 16 (24)   | .016    |
| PR, n (%)       | 13 (22)  | 17 (26)   | .040    |
| SD, n (%)       | 29 (49)  | 25 (38)   | .047    |
| PD, n (%)       | 10 (17)  | 8 (12)    | .042    |

0 = confidence interval, ORR = complete response, LTENS-ATZ = long-term extended nursing services plus atezolizumab, LTNC-ATZ = long-term conventional nursing plus atezolizumab, CR = objective response rate, PD = progressive disease, PR = partial response, SD = stable disease.

### Table 5
The comparison of TRAEs between LTENS-ATZ and LTNC-ATZ group.

| Groups          | LTNC-ATZ | LTENS-ATZ | P value |
|-----------------|----------|-----------|---------|
| All grade, n (%) | 35 (58)  | 24 (36)   | .014    |
| Fatigue         | 16 (27)  | 10 (15)   | .022    |
| Rash            | 3 (5)    | 2 (3)     | >.1     |
| Pyrexia         | 3 (5)    | 1 (2)     | >.1     |
| Arthralgia      | 4 (7)    | 1 (2)     | >.1     |
| Decreased appetite | 6 (10)  | 2 (3)     | .042    |
| Nausea          | 6 (14)   | 3 (5)     | .014    |
| Diarrhea        | 5 (8)    | 2 (3)     | .037    |
| Pruritus        | 5 (8)    | 1 (2)     | .048    |
| Vomiting        | 4 (7)    | 2 (3)     | .046    |
| Anemia          | 2 (3)    | 1 (2)     | >.1     |
| Pneumonitis     | 2 (3)    | 1 (2)     | >.1     |
| Hypotension     | 1 (2)    | 1 (2)     | >.1     |
| Hypertension    | 1 (2)    | 1 (2)     | >.1     |
| Colitis         | 1 (2)    | 1 (2)     | >.1     |
| Grade 3–4, n (%) | 9 (15)   | 4 (6)     | .025    |

LTENS-ATZ = long-term extended nursing services plus atezolizumab, LTNC-ATZ = long-term conventional nursing plus atezolizumab, TRAEs = treatment-related adverse events.

### 3.6. The comparison of renal function between LTENS-ATZ and LTNC-ATZ group

The renal function was evaluated in patients between LTENS-ATZ and LTNC-ATZ group. As shown in Figure 2, compared with LTENS-ATZ, LTENS-ATZ improved renal function including serum creatinine, BUN, albumin, and eGFR (P < .05).

### 3.7. The comparison of survival and occurrence between LTENS-ATZ and LTNC-ATZ group

Survival and occurrence rate was compared for bladder cancer patients after endoscopic bladder resection between LTENS-ATZ and LTNC-ATZ group. As shown in Figure 3A, patients in LTENS-ATZ group had higher survival rate than that in LTNC-ATZ group. During 36-month follow up, outcomes demonstrated that patients in LTENS-ATZ group had lower occurrence rate than that in LTNC-ATZ group (Fig. 3B). The difference in survival and occurrence rate was statistically significant (P < .05). There were no treatment-related deaths.

### 4. Discussion

Nursing services combined with clinical anti-cancer treatments plays an important role in improving the confidence of patients, anxiety, depression, health-related quality of life and survival of patients.[23-26] In general, ATZ has been well tolerated in bladder cancer patients, with most adverse events being mild to moderate in grade. This study evaluated the effect of LTENS-ATZ on renal function in patients with bladder cancer after endoscopic bladder resection. The results of this clinical study show that LTENS increased the anti-tumor responses of ATZ in patients with bladder cancer after endoscopic bladder resection whose tumors have positive PD-L1 expression. This trial included patients with bladder cancer after extended bladder resection and notably, the median duration of response had been reached in a median follow-up of 36 months. The high survival and low incidence of patients in LTENS-ATZ group makes the importance of LTENS in clinical bladder cancer patient who received endoscopic bladder resection.

Since the development of nursing services, there have been major improvements in the postoperative rehabilitation for patients with bladder cancer. Extended nursing services enlarge the content and scope of normal nursing, which have a significant effect in the treatment and recovery of cancer patients. Currently, anti-cancer treatment with methotrexate, vinblastine, doxorubicin, and cisplatin chemotherapy 30 years ago, there have been no major improvements in the treatment outcomes for patients with urothelial carcinoma. This study firstly explored the effect of long-term extended nursing services combined with ATZ in bladder cancer patient who received endoscopic bladder resection. Compared with extended nursing services, long-term extended nursing services combined with anti-cancer therapy of ATZ could further decrease follow-up compliance post hospitalization and improved quality of life. Consistently, long-term extended nursing services decreased length of hospital stay, the anxiety and depression for patients after endoscopic bladder resection. Notably, outcomes firstly indicated that LTENS-ATZ increased survival rate and decreased the occurrence rate for bladder cancer patient who received endoscopic bladder resection.

Clinically, ATZ is effective drug for patients in earlier bladder cancer stages and in the first-line metastatic setting.[27] Evidences from phase I and II trials suggest durable activity of ATZ in advanced bladder cancer, which has progressed during or after chemotherapy.[28] Data in this study confirmed the safe and efficacy of ATZ and found that LTENS decreased the drug discomfort and treatment-related adverse events in patients.
with bladder cancer after endoscopic bladder resection. Phase I trial shows that the objective response rates was 28% and 42% for the high/moderate PD-L1 group and upper tract primary tumors, respectively.\[29\] Interestingly, data in the current study indicated that LTENS increased the response rate (58.0% vs 43.2%) compared with LTNC for patients with bladder cancer after endoscopic bladder resection. A Phase II trial has showed that the median overall survival time was 14.8 months and 1-year overall survival rate was 57% for patients who had bladder cancer metastases and received ATZ treatment.\[30\] Importantly, compared with a previous study, both LTENS and LTNC increased the median survival time and rate of bladder cancer patients. Moreover, LTENS-ATZ improved the renal function and decreased the occurrence rate compared to those patients in LTENS-ATZ group. This efficacy of LTENS-ATZ may contribute to the postoperative rehabilitation therapy for bladder cancer patients.

5. Conclusion
In conclusion, outcomes in this study indicate that LTENS-ATZ not only improves the anxiety, depression, postoperative complications and increased satisfaction and the quality of life, as well as ameliorates investigator-assessed response rates, treatment-related adverse events, renal function, and survival time and occurrence rate in patients with bladder cancer after endoscopic bladder resection. This efficacy of LTENS-ATZ provides a promising postoperative rehabilitation for patients with bladder cancer.

Author contributions
YS and PJR performed all experiments in the present study. YW, BDZ, and JRW analyzed the experimental data. YL designed all experiments in the present study.

Conceptualization: Yao Song, Pengjuan Ren, Yue Li.
Data curation: Yao Song, Pengjuan Ren, Baodi Zhang.
Funding acquisition: Yang Wu, Junrong Wang.
Investigation: Yao Song, Pengjuan Ren, Yang Wu, Baodi Zhang, Junrong Wang, Yue Li.
Methodology: Pengjuan Ren, Baodi Zhang, Junrong Wang.
Project administration: Baodi Zhang, Yue Li.
Resources: Yao Song, Junrong Wang, Yue Li.
Software: Yao Song, Junrong Wang.
Supervision: Yang Wu, Baodi Zhang, Yue Li.
Validation: Yao Song, Yang Wu.
Visualization: Yang Wu.
Writing – original draft: Yue Li.
Writing – review & editing: Yue Li.

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