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CLINICAL INVESTIGATION

Efficacy and Safety of Bladder Preservation Therapy in Combination with Atezolizumab and Radiation Therapy (BPT-ART) for Invasive Bladder Cancer: Interim Analysis from a Multicenter, Open-label, Prospective Phase 2 Trial

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Purpose: To evaluate the safety and pathologic complete response (pCR) rate of radiation therapy with atezolizumab as bladder-preserving therapy for invasive bladder cancer.

Methods and Materials: A multicenter, phase 2 study was conducted with patients with clinically T2-3 or very-high-risk T1 bladder cancer who were poor candidates for or refused radical cystectomy. The interim analysis of pCR is reported as a key secondary endpoint ahead of the progression-free survival rate primary endpoint. Radiation therapy (41.4 Gy to the small pelvic field and 16.2 Gy to the whole bladder) was given in addition to 1200 mg intravenous atezolizumab every 3 weeks. After 24 treatment weeks, response was assessed after transurethral resection, and tumor programmed cell death ligand-1 (PD-L1) expression was assessed using tumor-infiltrating immune cell scores.

Results: Forty-five patients enrolled from January 2019 to May 2021 were analyzed. The most common clinical T stage was T2 (73.3%), followed by T1 (15.6%) and T3 (11.1%). Most tumors were solitary (77.8%), small (<3 cm) (57.8%), and without concurrent carcinoma in situ (88.9%). Thirty-eight patients (84.4%) achieved pCR. High pCR rates were achieved in older patients (90.9%) and in patients with high PD-L1−expressing tumors (95.8% vs 71.4%). Adverse events (AEs) occurred in 93.3% of patients, with diarrhea being the most common (55.6%), followed by frequent urination (42.2%) and dysuria (20.0%). The frequency of grade 3 AEs was 13.3%, whereas no grade 4 AEs were observed.

Conclusions: Combination therapy with radiation therapy and atezolizumab provided high pCR rates and acceptable toxicity, indicating it could be a promising option for bladder preservation therapy.

Introduction

Bladder cancer (BC) is one of the most frequent life-threatening urologic malignancies within the elderly.[1] Radical cystectomy (RC), an invasive procedure, is the gold standard treatment for patients with muscle invasive bladder cancer (MIBC) and very-high-risk, nonmuscle invasive bladder cancer (NMIBC) as malignant as MIBC.[2−4] However, RC using urinary diversions, such as ileal conduit or orthotopic neobladder, is so physically and psychologically invasive that some patients refuse or cannot tolerate the surgery because of the negative consequences for quality of life. Bladder preservation therapy (BPT) is attractive and recommended for patients who have either refused RC or are poor candidates for it owing to complications.[2−5] Recently, BPT has been recognized as an option clinically in equipoise with RC.[2−5]

Bladder preservation therapy is performed in a multimodal approach with an initial maximal transurethral resection of bladder tumor (TURBT), followed by radiation therapy (RT) and concurrent chemotherapy. The standard radiosensitizers of use in MIBC are 5-FU and mitomycin, cisplatin, or carbogen and nicotinamide.[2−6] Previous studies of BPT featuring chemoradiation therapy showed 5-year overall survival (OS) rates of 48% to 57% and pathologic complete response (pCR) rates of 72% to 83%.[7−12] Recently, BPT has been further improved by ideal indications, refinements in surgical procedure, advances in RT techniques, chemotherapy (with cisplatin as the radiosensitizer), and patient selection.[13] The standard of care for localized MIBC in patients either unwilling to receive or unfit for RC is trimodality therapy, usually featuring immune-modulating drugs. These immune checkpoint inhibitors (ICIs) have also been approved for urothelial carcinoma, because diverse clinical trials have shown safety and efficacy even in elderly patients.[14−21] Combinations of ICIs and RT are considered synergistic, as evidenced by the abscopal effect, where RT induces cancer antigen release from necrotic tumor tissue to activate cytotoxic T lymphocytes.[22,23] This combination is also currently under exploration in several clinical trials for BPT.[24]

Here, we offer, to our knowledge, the first efficacy and safety report on such a trial for BPT, featuring a combination of RT and atezolizumab (human programmed death ligand 1 [PD-L1] inhibitor), in patients with BC who could not tolerate or who refused RC.

Methods

Study design and participants

The Bladder Preservation Therapy in Combination with Atezolizumab and Radiation Therapy for Invasive Bladder Cancer (BPT-ART) trial was a multicenter, open-label, single-arm phase 2 study conducted at 9 hospitals. Investigators referred this study treatment to patients who consented to participate after receiving explanations that trimodality therapy is the standard of care.

Eligible patients were 20 years of age or older with an Eastern Cooperative Oncology Group performance status score of 0 or 1, had undergone TURBT within 90 days before enrollment, and had a tissue diagnosis of urothelial carcinoma (including other histologic types). These patients were also previously diagnosed with invasive bladder cancer with a histologic TNM classification (Union for International Cancer Control / American Joint Committee on Cancer staging manual, 8th edition) as follows: (1) patients with T2-3N0M0; (2) patients with T1N0M0 (very-high-risk group T1) who met at least 1 of the following criteria: multiple T1 tumors, residual T1 tumor on the tissue of the second TURBT, complicated by broad carcinoma in situ (CIS), and/or bacille calmette-guerin -resistant or intolerant. T1 cases were limited to a maximum of 8 out of a total of 45 expected cases, based on estimates of the number of cases with bladder preservation experience at participating facilities.

Exclusion criteria were a maximum tumor diameter of 5 cm or more, T4 tumors, concurrent upper urinary tract or urethral tumors, hydronephrosis, active malignancy within the past 5 years, or a history of active autoimmune disease or complications. Systemic corticosteroids (prednisone equivalent $\geq$ 10 mg/d) or immunosuppressive therapy; prior treatment with anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies; prior RT to the pelvic region; active hepatitis B or C; and/or HIV infection were additional exclusion criteria.

The study was conducted in accordance with the Declaration of Helsinki or its equivalents. Written informed consent was provided by all patients. The protocol and all revisions were approved by the institutional review board or ethics committee of each participating institution. The study is registered in the Japan Registry of Clinical Trials (jRCT2031180060) and was conducted from January 2019 to June 2024. The final survival follow-up period is scheduled at the completion of the study.

Protocols

The study protocol was composed of 3 parts: atezolizumab combination with RT, pathologic assessment at 24 weeks after initiation of treatment, and atezolizumab maintenance as described in the previous protocol paper.[25]

ICI-RT protocol

Patients received repeated intravenous doses of the study drug atezolizumab (1200 mg/body) 60 minutes every 3 weeks for 8 cycles. At the start of atezolizumab treatment, patients received 41.4 Gy/23 fr of RT to the small pelvis, including the pelvic lymph nodes but not the common iliac lymph nodes, and an additional 16.2 Gy/9 fr to the whole bladder using the box technique with 4 beams. The pelvic field borders were typically as follows: 1.5 cm laterally from the pelvic cavity, inferiorly to the ischial tuberosities, superior at the L5/S1 interspace, posteriorly to the sacrum (not including the area around the coccyx), and anteriorly to the pubic symphysis. To reduce the gastrointestinal dose for all patients, it was recommended that a full bladder protocol be used for small pelvis irradiation and an empty bladder for boost irradiation. Three-dimensional conformal RT planning and image guidance were performed.

Assessment

Every 12 weeks, patients were evaluated by CT scan and cystoscopy for recurrence, progression, and events. At 24 weeks after treatment start, patients underwent transurethral bladder biopsy or resection for histologic evaluation. Patients with pCR or residual tumors with less than pT1 scoring were transferred to a maintenance protocol.

Maintenance protocol

Patients received 7 cycles of repeated doses of atezolizumab the same as in the ICI-RT protocol phase.

Outcomes

The primary endpoint of this study was progression-free survival (PFS), and a key secondary endpoint was the pCR rate after 24 weeks of study drug administration. Other secondary endpoints were recurrence-free survival (RFS), OS, bladder preservation rate, and duration of response. This interim analysis was planned to be performed in the protocol and assessed the pCR rate after 24 weeks, PD-L1 expression, and acute adverse events up to 12 weeks after completion of RT. The pCR was determined based on histologic evaluation by a central pathologist and radiologic assessment according to Response Evaluation Criteria in Solid Tumors guidelines, version 1.1, at each institution. Safety was monitored through medical records evaluated by investigators using scoring from the Japanese translation of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Immunohistochemistry analyses

Tissue section (4 μm thick) samples from formalin-fixed and paraffin-embedded blocks were collected from patients who underwent TURBT before study treatment. Expression of PD-L1 protein on tumor-infiltrating immune cells (ICs) was detected by immunohistochemical staining using the human monoclonal antibody SP142 (Ventana) and assessed by IC scores with diagnostic levels of 0, 1, 2, or 3.

Statistical analyses

The number of enrolled cases was set at 45. Assuming a threshold of 45% as the 3-year PFS rate, an expected rate of 70%, and success probability of the primary analysis set as 80%, the sample size was set at 34 cases, and the loss of information rate was estimated to be about 25%. The exact binomial test for the pCR for the study treatment after 24 weeks was conducted with a null hypothesis of 60.0%, referring to pCR of RT alone. The 95% confidence intervals (CIs) for the pCR rate were investigated by using an exact confidence interval based on a binomial distribution with the use of the Clopper-Pearson exact method. All statistical tests were conducted on 2-tailed hypotheses, with a significance level of .05. SAS, version 9.4, was used for all statistical analyses (SAS Institute, Cary, North Carolina).

Results

Patient characteristics and protocol achievement

Of 54 patients who were assessed for eligibility, 46 patients were enrolled between January 2019 and May 2021. A total of 45 patients were analyzed, and Table 1 summarizes their characteristics at baseline. The median age was 71 years

Table 1 Patient characteristics

Characteristic	Patients (N = 45)*
Age, median (range), y	71.0 (39-83)
Sex	
Male	35 (77.8)
Female	10 (22.2)
Smoking history	
No	14 (31.1)
Yes	31 (68.9)
ECOG performance status score	
0	41 (91.1)
1	4 (8.9)
Charlson Comorbidity Index	
<5	19 (42.2)
≥5	26 (57.8)
History of upper urinary tract cancer	
No	45 (100.0)
Yes	0
History of bladder cancer	
No	34 (75.6)
Yes	11 (24.4)
Histology type	
Pure UC	40 (88.9)
UC with glandular differentiation	1 (2.2)
UC with squamous differentiation	2 (4.4)
UC with sarcomatoid variant	1 (2.2)
UC with glandular differentiation and plasmatoid variant	1 (2.2)
Clinical T stage at time of enrollment	
T1	7 (15.6)
T2	33 (73.3)
T3	5 (11.1)
Multiple	
No	35 (77.8)
Yes	10 (22.2)
Tumor size, cm	
<3	26 (57.8)
3-5	19 (42.2)
Concomitant CIS	
No	40 (88.9)
Yes	5 (11.1)
Complete resection at time of enrollment	
No	7 (15.6)
Yes	30 (66.7)
Unknown	8 (17.8)
Baseline PD-L1 expression	
IC 0, <1%	21 (46.7)
IC 1, 2, or 3, ≥1%	24 (53.3)
Neutrophils at baseline, median (range), No.	4049 (1765-6994)
Lymphocytes at baseline, median (range), No.	1605 (686-3071)
Baseline NLR, median (range)	2.2 (1.1-4.7)

Abbreviations: CIS = carcinoma in situ; ECOG = Eastern Cooperative Oncology Group; IC = immune cell score; NLR = neutrophil-lymphocyte ratio; PD-L1 = programmed cell death ligand-1; UC = urothelial carcinoma.

* Data are presented as the number (percentage) of patients unless otherwise specified.

(range, 39-83 years), and most patients (77.8%) were men. The number of patients with clinical T2-3 and T1 tumors were 38 (84.4%) and 7 (15.6%), respectively. Most tumors were single (77.8%), of small size (<3 cm) (57.8%), and without concomitant CIS (88.9%). More than half of the patients (66.7%) had undergone maximal TURBT at the time of enrollment. Eleven patients had a history of BC with experiences of bacille calmette-guerin intravesical administration (Table E1). Of 45 patients, 41 (91.1%) completed the ICI-RT protocol, but 4 patients discontinued treatment owing to adverse events (AEs) (n = 3) and progression of disease (PD) (n = 1). Only 1 patient could not complete the protocol owing to frequent urination caused by RT, whereas 2 patients were unable to complete the treatment phase of the study drug owing to an immune-related Adverse Events (irAE). The patient with PD developed distant lymph node metastasis during the ICI-RT period.

Efficacy outcomes

Our interim analysis included 45 patients allocated to the intervention, regardless of whether they had PD or had completed protocol treatment, as of the data cutoff on December 9, 2021 (Fig. 1). A total of 42 patients were assessed for pathologic response. Three patients could not be assessed: 2 had PD between ICI-RT and the pathologic response evaluation and 1 had PD during the ICI-RT period. Ultimately, pCR was confirmed in 38 patients, and the overall pCR rate was 84.4% (95% CI, 70.5%-93.5%), significantly higher than the prespecified pCR threshold ($P < .001$) (Fig. 1 and Table 2). Among the 7 patients without pCR, 4 had been assessed pathologically at 24 weeks by TURBT and had residual NMIBC tumors (1 with Ta and 3 with T1), whereas 3 patients had progression of disease. Of the 7 patients without pCR, 4 had clinical T2 tumors, 1 had a clinical T3 tumor, and 2 had clinical T1 tumors at the time of enrollment.

Table 2 shows the results of the pCR rate subgroup analysis. The pCR rates of patients with T2 (n = 29/33), T3 (n = 4/5), and T1 (n = 5/7) tumors were 87.9% (95% CI, 71.8%-96.6%), 80.0% (95% CI, 28.4%-99.5%), and 71.4% (95% CI, 29.0%-96.3%), respectively. Of note, patients aged 75 years or older achieved a pCR rate of 90.9% (95% CI, 58.7%-99.8%), similar to that of younger patients. Furthermore, the pCR rates in the subgroup of patients who achieved complete resection at the time of enrollment were similarly high (90.0%; 95% CI, 73.5%-97.9%). The subgroup of patients with concomitant CIS had a pCR rate of 60.0% (95% CI, 14.7%-94.7%), as did patients with multiple tumors (70.0%; 95% CI, 34.8%-93.3%). In terms of the neutrophil-lymphocyte ratio, the pCR rates were similar in the low group (85.0%; 95% CI, 62.1%-96.8%) and the high group (82.6%; 95% CI, 61.2%-95.0%) by a median neutrophil-lymphocyte ratio cutoff of 2.2.

Regarding tumor PD-L1 expression levels at baseline, the subgroup of patients with IC scores of 1, 2, or 3 achieved

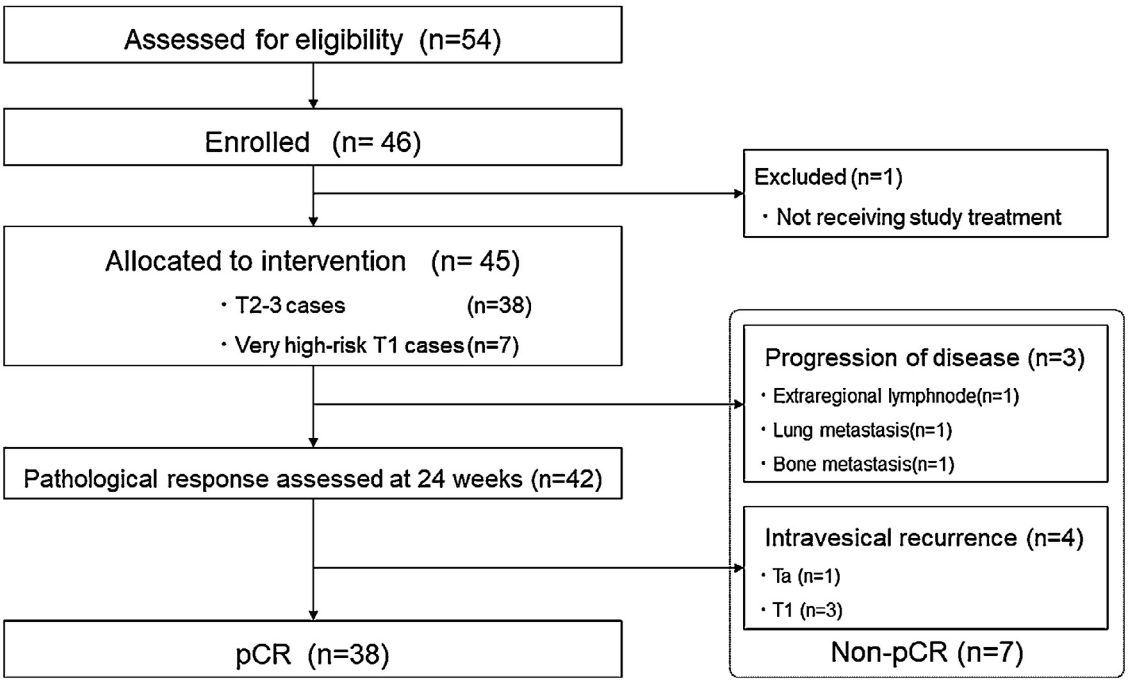

Fig. 1. Study flow chart.

high pCR (95.8%, 95% CI, 78.9%-99.9%), whereas the proportion of the pCR rates in the subgroup of patients with an IC score of 0 was low (71.4%, 95% CI, 47.8%-88.7%). The pCR rates in the group with high PD-L1 expression (IC > 1) were not significant but were higher than those in the low PD-L1 expression group (IC of 0) (95.8% vs 71.4%; $P = .389$).

Safety

Radiation therapy was completed according to protocol in 44 of 45 patients, and no patient stopped owing to RT AEs during the treatment period. The safety analysis was performed after a data cutoff on August 31, 2021. Table 3 summarizes acute AEs, which occurred in 93.3% of the patients; the proportions of AEs attributable to RT and atezolizumab were 82.2% and 44e.4%, respectively. The most frequent AE was diarrhea (55.6%), followed by pollakiuria (42.2%) and dysuria (20.0%), which are common acute AEs of RT (Table 4). Grade ≥3 AEs were observed in 6 patients (13.3%). In contrast, only 3 patients (6.6%) discontinued owing to AEs, which were radiation-related dysuria (grade 2), drug-related myocarditis (grade 2), or colitis (grade 3).

Discussion

We evaluated the clinical efficacy of a single PD-L1 inhibitor (atezolizumab) in combination with RT in BPT for patients with BC who either refused RC or who were not candidates for it owing to complications. The key secondary endpoint of pCR rate at 24 weeks after protocol treatment was 84.4% based on interim analysis. The pCR rates of the patients treated with RT alone versus chemoradiation therapy were 44% to 61%[26–29] and 70% to 85%,[9,30–34] respectively. These results might suggest that RT and ICI combinations are attractive for BPT and a useful alternative to chemoradiation therapy in selected patients with BC. For ICI monotherapy as a neoadjuvant therapy before RC, the rates of pCR and down-staging to pT2 or less were 34% to 46% and 39% to 58%, respectively.[15,21,35,36] We thus speculate that RT could further enhance the effectiveness of ICIs, leading to adequate pCR rates in BPT as well as other applicable cancers.[36] The total dose in this study was 57.6 Gy, aimed to optimize the balance between safety and efficacy. Regarding safety, prophylactic pelvic irradiation was mandatory in this study; however, few reports exist on the safety of the concurrent use of ICIs with prophylactic pelvic irradiation. In addition, the PLUMMB trial,[37] which evaluated sequential RT with pembrolizumab plus hypofractionated radiation, was paused owing to dose-limiting toxicity. We expected an enhancement of local effect by the concurrent use of atezolizumab. Thus, the present study is, to our knowledge, the first report of a phase 2 clinical trial of BPT indicating that the combination of atezolizumab and RT is a promising strategy for selected patients with MIBC.

Very-high-risk NMIBCs are rapidly progressive and mandate a cure-focused approach similar to MIBCs.[3] In this study, 7 patients with very-high-risk NMIBC were enrolled, and 5 achieved pCR (71.4%; 95% CI, 29.0%-96.3%). Two had residual NMIBC but continued maintenance treatment because there were neither signs of MIBC progression nor distant metastases. Although reports of BPT for very-high-risk NMIBC are scarce, a meta-analysis of BPT with chemoradiation therapy for NMIBC showed a pCR rate of 78.2%

Table 2 Results of the pCR rate subgroup analysis

Variable	No./total No.	pCR rate (95% CI)
Overall	38/45	84.4 (70.5-93.5)
Age, y		
<75	28/34	82.4 (65.5-93.2)
≥75	10/11	90.9 (58.7-99.8)
Sex		
Male	29/35	82.9 (66.4-93.4)
Female	9/10	90.0 (55.5-99.7)
Smoking history		
No	12/14	85.7 (57.2-98.2)
Yes	26/31	83.9 (66.3-94.5)
ECOG performance status score		
0	34/41	82.9 (67.9-92.8)
1	4/4	100.0 (39.8-100.0)
History of bladder cancer		
No	28/34	82.4 (65.5-93.2)
Yes	10/11	90.9 (58.7-99.8)
Histologic variant		
No	34/40	85.0 (70.2-94.3)
Yes	4/5	80.0 (28.4-99.5)
Clinical T stage at time of enrollment		
T1	5/7	71.4 (29.0-96.3)
T2-3	33/38	86.8 (71.9-95.6)
Multiple		
No	31/35	88.6 (73.3-96.8)
Yes	7/10	70.0 (34.8-93.3)
Tumor size, cm		
<3	21/26	80.8 (60.6-93.4)
≥3	17/19	89.5 (66.9-98.7)
Concomitant CIS		
No	35/40	87.5 (73.2-95.8)
Yes	3/5	60.0 (14.7-94.7)
Complete resection at time of enrollment		
No	5/7	71.4 (29.0-96.3)
Yes	27/30	90.0 (73.5-97.9)
Unknown	6/8	75.0 (34.9-96.8)
Completion of radiation therapy		
No	1/1	100.0 (2.5-100.0)
Yes	37/44	84.1 (69.9-93.4)
Completion of drug administration		
No	2/3	66.7 (9.4-99.2)
Yes	36/42	85.7 (71.5-94.6)
Baseline PD-L1 expression		
IC 0	15/21	71.4 (47.8-88.7)
IC 1, 2, or 3	23/24	95.8 (78.9-99.9)
Baseline NLR		
Low	17/20	85.0 (62.1-96.8)
High	19/23	82.6 (61.2-95.0)

Abbreviations: CIS = carcinoma in situ; ECOG = Eastern Cooperative Oncology Group; IC = immune cell score; NLR = neutrophil-lymphocyte ratio; pCR = pathologic complete response; PD-L1 = programmed cell death ligand-1.

Table 3 Summary of adverse events

Adverse event	Patients, No. (%) (N = 45)
Any	42 (93.3)
Radiation-related	37 (82.2)
Drug-related	20 (44.4)
Drug- and radiation-related	2 (4.4)
Grade ≥3	6 (13.3)
Leading to discontinued intervention	3 (6.6)

(95% CI, 69.4%-r87%), a 5-year recurrence-free survival rate of 54% (95% CI, 38.1%-70%), a cancer-specific survival rate of 86% (95% CI, 80%-92%), and OS of 72% (95% CI, 64%-79%).[38] As such, our results also support future inclusion of NMIBC in studies with BPT that includes ICIs and RT.

Some clinical factors were considered to influence the observed success rates of BPT with our combination protocol. Appropriate indications for BPT include small size, solitary tumors, low clinical T stage, no CIS, no hydronephrosis, complete TURBT, and response to chemoradiation therapy, among others.[9,13,39–41] In this study, we enrolled only those patients who were relatively suitable for BPT; patients who had tumors more than 5 cm in diameter or patients with hydronephrosis were excluded. Additionally, a high percentage of patients (66.7%) achieved complete TURBT before enrollment in this study. Because the 3 cases that resulted in PD were all in patients with clinical T2 tumors at the time of registration, it seems possible to expect pCR even in patients with T3 disease if other conditions are met. There were no significant differences in pCR results with regard to age, gender, performance status score, history of bladder cancer, or histologic type, but 2 of the 5 patients with concomitant CIS had recurrent disease. Our results indicate that pCR-related clinical factors for BPT featuring ICIs with RT are similar to those for BPT featuring chemoradiation therapy. One putative reason is careful screening and enrollment based on well-known prognostic factors in favor of BPT with chemoradiation therapy.

To discuss the efficacy of ICIs, it is important that the immune environment, including PD-L1 expression and immune cells, is considered. Several clinical trials showed that patients with esophageal cancer with high PD-L1 expression had longer PFS and OS[42–44]; however, controversy exists in reports on patients with lung cancer.[45,46] On the other hand, promising results have been reported on BC and esophageal cancer treated by a combination of ICIs and RT.[47,48] In this study, we observed that the pCR rates in the group with high PD-L1 expression were higher compared with the low-expression group, suggesting that tumor PD-L1 expression might potentially be a clinically useful biomarker for predicting response in patients treated with our protocol. However, further randomized clinical trials are necessary for determining the correlation between tumor PD-L1 expression and treatment efficacy.

Table 4 Adverse events observed in >5% of all patients

Adverse event	Grade 1, No.	Grade 2, No.	Grade 3, No.	Total, No. (%)
Diarrhea	19	5	1	25 (55.6)
Pollakiuria	13	6	0	19 (42.2)
Dysuria	6	3	0	9 (20.0)
Pyrexia	6	2	0	8 (17.8)
Hepatic function abnormal	6	0	0	6 (13.3)
Decreased white blood cell count	4	1	1	6 (13.3)
Fatigue	5	0	0	5 (11.1)
Anemia	3	1	0	4 (8.9)
Cystitis	2	2	0	5 (8.9)
Decreased lymphocyte count	0	3	1	6 (8.9)
Malaise	4	0	0	7 (8.9)
Pruritus	4	0	0	8 (8.9)
Soft feces	3	1	0	9 (8.9)
Constipation	2	1	0	3 (6.7)
Micturition urgency	3	0	0	4 (6.7)
Nausea	3	0	0	5 (6.7)
Decreased appetite	3	0	0	6 (6.7)

There have been limited reports on the safety of RT with ICIs for bladder cancer. In a nonrandomized, prospective phase 1 trial, BPT (consisting of concurrent atezolizumab and gemcitabine plus hypofractionated RT) was reported to cause unacceptable gastrointestinal toxic effects.[49] Although that study irradiated only the bladder and lymph nodes (and did not include the pelvis), our protocol treatment included small pelvis irradiation of 41.4 Gy concurrently with atezolizumab, and our severe AE rate of only 13.3% indicated an acceptable safety and severity profile. Although the toxicity profiles were comparatively different, our observed proportion of severe AEs was similar to the 16% rate reported in the IMVigor210 trial, which used atezolizumab alone and no RT.[50] Possible reasons for the tolerability of AEs in this study include the fact that ICIs were not combined with chemotherapy, bladder conditions were optimized to reduce the gastrointestinal dose, and the total dose was set to 57.6 Gy (radical but slightly lower than in previous studies).[8,9]

This study had a single-arm, phase 2 design, short follow-up period, and exploratory determination of the utility of ICIs plus RT for BPT plus a biomarker analysis. Clinical benefit should be evaluated after PFS results, which was set as the primary endpoint of this trial. Despite these limitations, the results of this study demonstrated that RT plus atezolizumab has promising antitumor activity and an acceptable acute safety profile for BPT. This initial analysis provides a solid foundation for further investigation of new BPT paradigms featuring RT combined with ICIs for patients with MIBC and NMIBC.

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