Letter to the Editor

Disease progression in Bacillus Calmètte Guerin unresponsive non-muscle invasive bladder cancer patients with carcinoma *in situ*, participating in clinical trials on bladder-sparing treatment

Olga M. Pijpers^, Joost L. Boormans^

Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence to: Prof. Joost L. Boormans, MD, PhD. Department of Urology, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. Email: j.boormans@erasmusmc.nl.

Submitted Dec 22, 2023. Accepted for publication Feb 19, 2024. Published online Mar 25, 2024.
doi: 10.21037/tau-23-672
View this article at: https://dx.doi.org/10.21037/tau-23-672

Bladder-sparing treatment option for Bacillus Calmètte Guerin (BCG) unresponsive non-muscle invasive bladder cancer (NMIBC) patients is an unmet clinical need (1). Radical cystectomy (RC) is the recommended treatment option, according to current guidelines but many patients are unwilling or unfit to undergo radical surgery (2). Given the lack of alternative standard-of-care, the United States Food and Drug Administration (FDA) allowed single-armed study designs in the BCG-unresponsive setting as a randomized trial with RC or placebo as a comparator was not deemed feasible neither ethical (3,4). As a result, several single-arm clinical trials on bladder-sparing treatments in BCG-unresponsive NMIBC have been published in recent years. This has led to FDA approval of pembrolizumab and nadofaragene firadenovec for BCG-unresponsive carcinoma in situ (CIS) of the bladder. Nevertheless, the European Association of Urology (EAU) guidelines on NMIBC, states "*At the present time*, *treatments other than radical cystectomy are considered oncological inferior in patients with BCG-unresponsive disease*" (2). The rationale for this is that bladder-sparing treatments lead to delay of definitive RC, which might put patients at risk of developing disease progression. The survival outcome of NMIBC patients who develop disease progression to muscle-invasive disease is poor and therefore bladder-sparing treatment in BCG-unresponsive NMIBC is considered oncological inferior to RC (2,5). The aim of the present study is to evaluate the risk of disease progression in patients with BCG-unresponsive CIS of the bladder who were enrolled in clinical trials on bladder-sparing treatments.

Four prospective phase II/III clinical trials on bladder-sparing treatments for BCG-unresponsive CIS of the bladder have been reported. The drugs of investigation were: intravesical nadofaragene firadenovec gene therapy (NCT02773849), pembrolizumab monotherapy (KEYNOTE-057, NCT02625961), IL-15 Superagonist Nogapendekin alfa inbakicept (NAI) in combination with BCG (QUILT-3.032, NCT03022825) and atezolizumab (SWOG S1605, NCT02844816) (6-9). The clinicopathological characteristics of the study populations are depicted in *Table 1*. All studies defined progression of disease as development of muscle-invasive bladder cancer (MIBC), stage ≥ T2. In the NAI + BCG trial, disease progression from CIS to T1 stage was also considered progression (trial protocol), whereas in the pembrolizumab trial cancer of the upper urinary tract was considered as progression (7,8). The number of patients who developed progression during or immediately after the treatment under investigation was 3 out of 96 in the pembrolizumab trial, and 4 out of 74 in the atezolizumab study (8,9). The corresponding median follow-up was 36 versus 41 months (8,9). Progression-free survival (PFS) was 97% in the pembrolizumab trial and for patients receiving NAI + BCG 88% overall versus 91% for responding patients (7,8). In the nadofaragene firadenovec trial, a total of 30 patients underwent RC and the surgical resection

^ ORCID: Joost L. Boormans, 0000-0002-5127-0436; Olga M. Pijpers, 0000-0002-5392-4245.

Table 1 Progression outcomes of patients participating in phase II/III clinical trials investigating treatment efficacy and tolerability of bladder-sparing treatments in patients with BCG-unresponsive non-muscle invasive bladder cancer with carcinoma *in situ*

Study parameters	Nadofaragene firadenovec (6)	Pembrolizumab (8)	NAI + BCG (7)	Atezolizumab (9)
Number of patients	103	96	82	74
Median follow-up (months)	19.7 (IQR: 16.0–24.8)	36.4 (IQR: 32.0–40.7)	23.9 (range, 3.2–37.5)	41
Definition of disease progression				
Muscle-invasive bladder cancer	Yes	Yes	Yes	Yes
Lymph-node positive disease	NR	Yes	Yes	Yes
Metastatic disease	NR	Yes	Yes	Yes
Increase in stage from CIS to T1	NR	NR	Yes	NR
Upper tract urothelial carcinoma	NR	Yes	NR	NR
Progression-free survival[†]				
1-year	NR	Overall: 97% (95% CI: 86.0–99.2%)[†]	Overall: 88.4% (95% CI: 78.9–93.8%)[†] Responders: 91.1% (95% CI: 79.8–96.2%)[†]	NR
2-year	NR	NR	Overall: 84.7% (95% CI: 73.6–91.3%)[†] Responders: 88.1% (95% CI: 74.9–94.6%)[†]	NR
Total number of patients with disease progression	5[‡]	6[§]	NR	7[¶]
Progression during or immediately after bladder-sparing treatment				
Total	See notes[‡]	3	NR	4[¶]
≥ pT2 at RC	2[‡]	3	NR	4[¶]
TNM stage*	NR	pT2N0 pT2N1 pT3N1	NR	pT2aN0M0 pT3aN3M0 pT3bN2M0 ypT4bN1M0
Number of patients who underwent RC	30 at 12 months	40	Overall: 13 Responders: 5	27

Notes: *, TNM stage preceded by "p" refers to pathological staging at RC; [†], in both studies the definition of progression-free survival also included the absence of death; [‡], two patients were upstaged to ≥ pT2. For one patient pathological T-stage was unknown and one patient had a complete pathological response (pT0). One patient first had disease recurrence after nadofaragene, then started pembrolizumab and subsequently had progression of disease at RC (pT2N1). The pT-stage for this patient is not reported in the table as progression was not during or immediately after the bladder-sparing treatment under investigation; [§], three patients had progression of disease based on pathological staging. Three patients discontinued pembrolizumab cause of recurrence or no response but did not undergo RC but opted for alternative non-surgical therapies and later progressed to muscle-invasive bladder cancer or metastatic disease. All three patients experienced progression at least 1 year after study discontinuation (23, 29, and 20 months after last dose of pembrolizumab); [¶], as described in *Tables. S3,S4*, in total, seven patients had progression. In four patients, disease progression developed during or immediately after treatment with atezolizumab, whereas three patients had non-invasive recurrent disease, for which first alternative treatment was started (for two bladder-sparing for one RC) and thereafter developed progression. BCG, Bacillus Calmètte Guerin; NAI, Nogapendekin alfa inbakicept; IQR, interquartile range; NR, not reported; CIS, carcinoma *in situ*; CI, confidence interval; RC, radical cystectomy; TNM, tumor-node-metastasis.

specimen showed pathological upstaging to ≥ pT2 in three patients, including one patient with stage pT2N1 who first had tumor recurrence after nadofaragene firadenovec, then received pembrolizumab, and thereafter underwent RC because of progression (6). In the pembrolizumab trial, 40 patients underwent RC, of whom three had pathological upstaging to MIBC: stage pT2N0, pT2N1, and pT3N1 (8). The interval between the last pembrolizumab administration and RC was 60, 86, and 457 days, respectively. In the atezolizumab trial, seven patients experienced disease progression, including three patients who first had recurrence of disease, then received a second line of intravesical treatment (n=2) or RC (pTisN0) and thereafter developed disease progression (supplementary material) (9). Overall, 36% (27/74) of the patients underwent RC of whom four had MIBC; stage pT3N3 (33 days), pT3bN2 (122 days), pT4N1 (201 days), pT2N0 (353 days) from the start of atezolizumab. One patient developed distant metastasis without intravesical recurrence 462 days after atezolizumab.

Overall, the risk of disease progression in patients with BCG-unresponsive CIS of the bladder enrolled in clinical trials investigating bladder-sparing treatments was less than 7%. As such, in the majority of patients, RC appears to be postponed without jeopardizing oncological outcome. However, although the risk of progression is the reason for not recommending bladder-sparing treatment as standard-of-care in patients with BCG-unresponsive disease, progression was not the primary endpoint of the four reported clinical trials leading to heterogeneity between the studies on progression outcomes. This hampered concluding the risk of progression between different bladder-sparing treatments. To demonstrate, the definition of progression varied across the trials and the 1- and 2-year PFS was only reported in two out of four trials; pembrolizumab and BCG + NAI, and in both studies the definition for PFS also included the event of not bladder cancer-related death. In the nadofaragene firadenovec, pembrolizumab, and atezolizumab trials the proportion of patients with progression was reported. However, the varying median follow-up of 19.7 to 41 months hampered direct comparison, as the risk of progression increases with longer follow-up (6,9). This heterogeneity in definition and fixed endpoints was also previously stressed by the International Bladder Cancer Group (10). Additionally, patients who experienced disease recurrence after the treatment under investigation, subsequently started another line of bladder-sparing treatment, and thereafter developed progression of disease, were included in the total number of patients with progression. This resulted in an overrepresentation of the proportion of patients with progression in trials with longer follow-up. Pathological staging was reported in the nadofarag firadenovec, pembrolizumab, and atezolizumab trials. The atezolizumab trial provided supplementary material with elaborated information on all patients with progression to MIBC and metastatic disease (6,8,9). As not all patients with progression of disease will undergo RC, clinical staging carries additional information, but it is mandatory to report pathological staging for the subgroup of patients receiving RC as up- and downstaging is possible, and this affects survival outcomes (11). Off note, in clinical practice, whether the risk for progression justifies delaying RC also depends on patient-specific factors as: age, co-morbidities, the risk of peri-operative complications, and patient preferences, as the perioperative mortality rate of RC varies between 2% and 13% (12). Therefore, as stated in the EAU guideline on NMIBC, the decision to opt for RC or bladder-sparing treatment should be based on shared decision-making where information on the risk of progression is highly relevant (2).

In conclusion, the reported risk of progression of disease in patients with BCG-unresponsive CIS of the bladder enrolled in clinical trials on bladder-sparing treatments seems low. However, the definition of progression and median follow-up varied between the series precluding accurate interpretation. As such, we recommend consistent reporting on progression including a clear definition of progression and providing PFS at fixed endpoints. We believe the definition for progression could be: the development of histologically confirmed muscle-invasive disease (≥ pT2), either at transurethral resection of the bladder tumor or at RC, and/or radiologically confirmed lymph node-positive disease (≥ N1), and/or distant metastasis (≥ M1) during or immediately after the treatment under investigation and not having had another line of bladder-sparing treatment.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article has undergone external peer review.

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-672/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-672/coif). J.L.B. has the following potential conflicts of interest to report: consultancy/speaker's fee (all paid to Erasmus Medical Center) from Janssen, BMS, AstraZeneca, Merck AG/Pfizer, MSD, and Bayer; research collaboration from Merck AG/Pfizer, MSD, Janssen and VitroScan; payment for book writing from Astellas. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Pijpers OM, Boormans JL. Disease progression in Bacillus Calmètte Guerin unresponsive non-muscle invasive bladder cancer patients with carcinoma *in situ*, participating in clinical trials on bladder-sparing treatment. Transl Androl Urol 2024;13(3):479-482. doi: 10.21037/tau-23-672

