Systematic Review and Meta-Analysis of Response Rates in BCG-unresponsive Non–Muscle-Invasive Bladder Cancer: a Consensus Statement From the International Bladder Cancer Group

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Abstract

There is a critical need to establish reference response rates following bladder-sparing therapies administered in the setting of bacillus Calmete-Guerin (BCG)-unresponsive non–muscle-invasive bladder cancer (NMIBC). We sought to determine the efficacy of different interventions in recent trials accruing patients fulfilling the strict BCG-unresponsive definition established by the US Food and Drug Administration. We performed a systematic review and meta-analysis for clinical trials in the BCG-unresponsive disease space to include published and presented results. The primary endpoints were complete response rate for CIS±Ta/T1 tumors, recurrence-free rate for patients with papillary-only disease, and disease-free rate in studies enrolling both papillary CIS tumors (Ta/T1/CIS). I^2 was used for assessing heterogeneity. Eleven studies using 9 different therapeutic agents in a total of 909 patients with BCG-unresponsive NMIBC were identified. The resulting outcomes at 3, 6, and 12 months were 44%, 38%, and 25% complete response rate in CIS±Ta/T1 tumors; 73%, 58%, and 48% recurrence-free rate in papillary-only; and 48%, 22%, and 43% disease-free rate in combined Ta/T1/CIS, respectively. Relatively low levels of heterogeneity were observed amongst studies restricted to papillary-only or CIS±Ta/T1 tumors. Future randomized controlled studies are needed and will likely require stratification between papillary-only and CIS±Ta/T1 tumors.

Introduction

The decision of the United States Food and Drug Administration (FDA) to accept single-arm phase II/III clinical trials of novel agents for the treatment of BCG-unresponsive non–muscle-invasive bladder cancer (NMIBC) in tumors with CIS emphasizes the importance of reference efficacy rates to help frame the decision for approval. A previous systematic review that aimed to provide such reference benchmarks uncovered significant heterogeneity in patients enrolled in previous NMIBC clinical trials regarding the number and timing of intravesical BCG instillation and the pathology of the subsequent recurrent tumor[1]. One method to circumvent these barriers is to homogenize the study population by using the standard BCG-unresponsive definition adopted by the FDA in clinical trial design[2]. Results from recent trials enrolling such patients will provide context for the interpretation of emerging data from ongoing clinical trials conducted in the BCG-unresponsive space.

Key Words

Bacillus Calmete-Guerin, BCG, BCG-unresponsive, BCG refractory, BCG relapsing, bladder cancer

Competing Interests

None declared.

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Methods

We performed a systematic review and meta-analysis in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations. An updated search was performed using the previously published protocol (PROSPERO CRD42019130553)[1]. Full search protocol, study review methodology, risk of bias assessment, and data synthesis are presented in **Supplementary Appendix 1** (siuj.org). We included unpublished studies from phase II-III clinical trials presented at national urologic/oncology conferences that strictly accrued patients with BCG-unresponsive disease. The primary endpoints were complete response rate (CRR) for CIS±Ta/T1 tumors, recurrence-free rate (RFR) for patients with papillary-only disease, and disease-free rate (DFR) in studies enrolling both papillary (Ta/T1) and CIS-containing patients as previously described (Ta/T1/CIS)[1,2]. We performed a meta-analysis of proportions with command metaprop and inverse method with logit transformed proportions and sensitivity analysis. Information was pooled with a random effect meta-analysis according to the heterogeneity expected. I^2 was used for assessing heterogeneity.

Results

The initial search yielded 287 studies. After screening, 11 relevant studies were selected for analysis (**Figure 1**). Six studies were excluded in total. Four studies performed before the establishment of the BCG-unresponsive definition in 2015 were excluded as they enrolled patients with low-grade recurrences following BCG [3–6]. Another trial using CG0070 was excluded because of incomplete reporting[7]. One study was excluded because of the inclusion of BCG-intolerant patients rather than strictly those with BCG-unresponsive disease[8]. Studies with cohorts consisting of CIS-CIS±Ta/T1 tumors and papillary-only disease were analyzed separately, as previously described[9]. The included studies used 9 different therapeutic agents in a total of 909 patients with BCG-unresponsive NMIBC (**Table 1**). Of the reported study arms, 6 enrolled CIS±Ta/T1 tumors, 6 papillary-only tumors, and 4 Ta/T1/CIS tumors conjointly.

The primary endpoints for CIS±Ta/T1, Ta/T1, and Ta/T1/CIS are listed by timepoints following therapy in **Table 2** and illustrated in the forest plots in **Figure 2**. Only the durable 12-month CRR from QUILT 3.032 study[10] was used in the meta-analysis as this was the only timepoint unequivocally reported. By limiting the analysis to studies enrolling patients fulfilling the BCG-unresponsive definition, we found more uniform but divergent response rates within the CIS±Ta/T1 and papillary-only cohorts, with 3-month, 6-month, and 12-month benchmarks that can help to inform emerging data from ongoing studies. The only deviation was the 12-month CRR of 44% reported in the QUILT 3.032[10], increasing the overall 12-month CRR from 21% to 25% and the I^2 from 0% to 77% (**Figure 2**). In contrast, results from studies conglomerating durable response rates between the 2 cohorts were marked by higher heterogeneity, supporting the differential responsiveness to bladder-sparing treatment between CIS±Ta/T1 and papillary-only NMIBC. These results may reflect different molecular pathways leading to the development of CIS (originating from chromosome 9p+q loss and TP53 and RB mutations) and papillary tumors (originating from FGFR alterations and 9q loss)[11]. Alternatively, divergent response and recurrence rates likely also reflect the fact that papillary tumors are amenable to complete transurethral resection but CIS usually is not[12].

The lack of uniformity amongst trial results further underscores differences in the mechanisms of action between the investigational agents and indicate differences therapeutic efficacy. To further eliminate risks of bias and increase the rigor of the analysis, randomized controlled trials (RCT) are likely required in the future. As there is no universally accepted bladder-preserving therapy for BCG-unresponsive NMIBC, there is a need to standardize treatment used in the control arm. Recent FDA approval suggests pembrolizumab is an option; however, many consider its efficacy insufficient to offset the observed toxicity profile and the significant cost[13]. Intravesical gemcitabine/docetaxel has also been proposed as an alternative by some on the basis of "expert opinion," although its efficacy has not yet been established in prospective clinical trials. Moreover, shortages of BCG in many countries have hampered administration according to the SWOG protocol, limiting the number of patients fulfilling the BCG-unresponsive definition and creating a bottleneck for completing RCTs in this disease setting.

This is the first meta-analysis to investigate the available studies that meet the strict definition of the BCG-unresponsive NMIBC definition adopted by the FDA in 2018[2]. Our results demonstrate a weighted average CRR of 38% at 6 months and 25% at 12 months in CIS±Ta/T1 BCG-unresponsive NMIBC. Of all completed trials, only one[10] achieved the 50% 6-month and 30% 12-month thresholds previously proposed to be clinically relevant[14,15] Notably, CRRs observed in trials using the 2 currently FDA-approved agents, pembrolizumab and valrubicin, fell short of these benchmarks regarding the 12-month duration of response. Several agents tested in similarly designed single-arm trials are currently under review by the FDA

FIGURE 1.

Flow diagram of literature review for BCG-unresponsive non-muscle-invasive bladder cancer studies

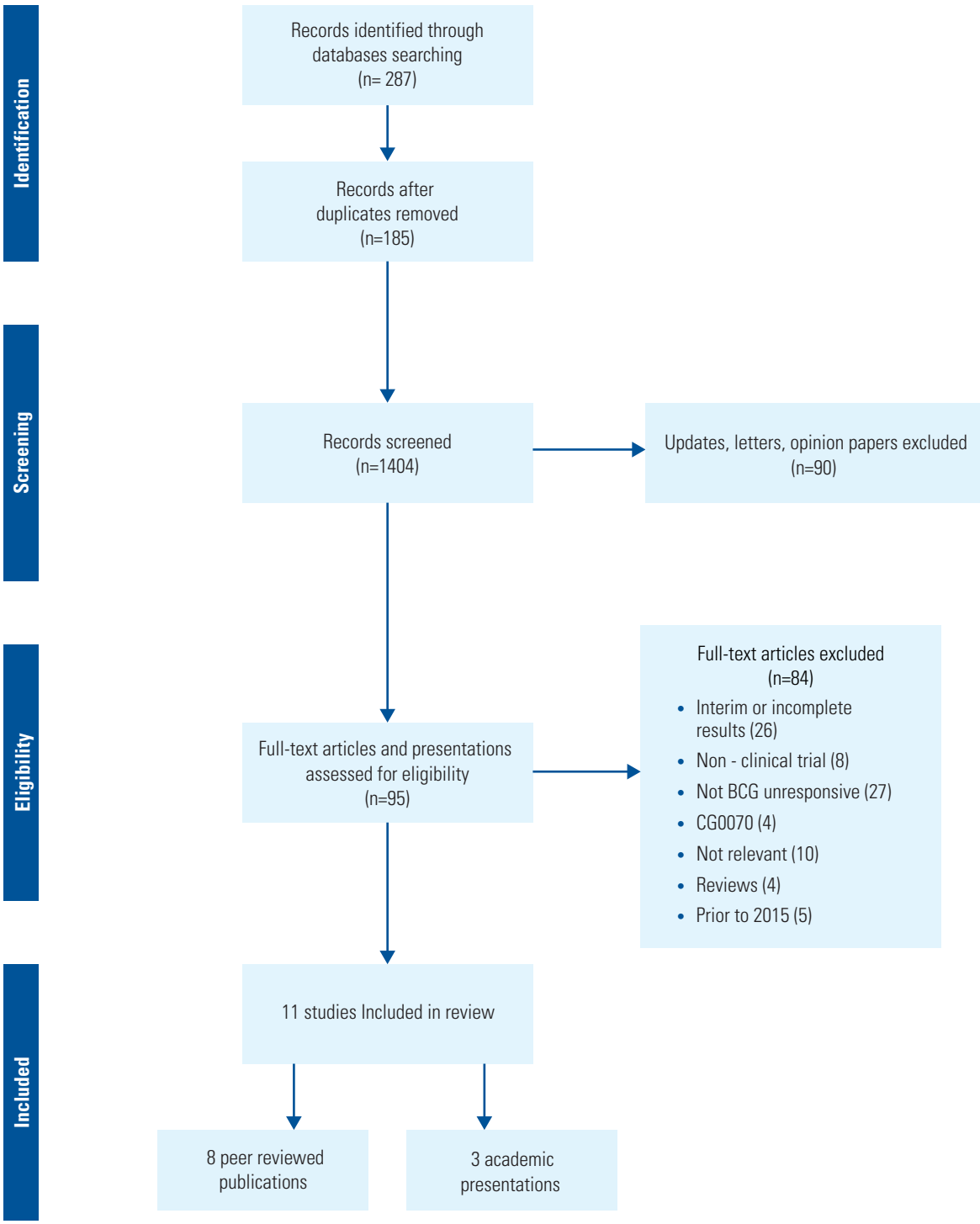


TABLE 1.

Presentations and publications in BCG-unresponsive NMIBC

Authors	Phase	Date of Publication or Presentation	Tumor Characteristics	Agent Administered
Navai et al. 2016[16]	I	2016	Ta/T1/CIS	Nadofaragene firadenovec
Hahn et al. 2017[17]	II	2017	Ta/T1/CIS	Dovitinib
Li et al. 2017[9]	II	2017	Papillary-only	MCNA[a]
Li et al. 2017[9]	II	2017	CIS±Ta/T1	MCNA[a]
Shore et al. 2017[18]	II	2017	Ta/T1/CIS	Nadofaragene firadenovec
O'Donnell et al. 2019[19]	II	2019	Papillary-only	CADI-05[b]
DeCastro et al. 2020[20]	I	2020	Ta/T1/CIS	Intravesical CGC[c]
Shore 2021[21]	III	2020	CIS±Ta/T1	Vicinium[d]
Shore 2021[21]	III	2020	Papillary-only	Vicinium[d]
Black et al. 2021[22]	II	2021	CIS±Ta/T1	Atezolizumab
Black et al. 2021[22]	II	2021	Papillary-only	Atezolizumab
Balar et al. 2021[23]	II	2021	CIS-containing	Pembrolizumab
Boorjian 2021[24]	III	2021	CIS±Ta/T1	Nadofaragene firadenovec
Boorjian 2021[24]	III	2021	Papillary-only	Nadofaragene firadenovec
Chang et al. 2022[10]	II/III	2022	CIS±Ta/T1	BCG + IL-15 Superagonist
Chang et al. 2022[10]	II/III	2022	Papillary-only	BCG + IL-15 Superagonist

[a] *Mycobacterium phei cell wall-nucleic acid complex* [b] *Intradermal CADI-05* [c] *Cabazitaxel, gemcitabine, cisplatin* [d] *rAd-IFNα/Syn3*

TABLE 2.

Meta-analysis results by tumor characteristic and months following administration

Time	CIS±Ta/T1 CRR (I^2)	Papillary-only Ta/T1 RFR (I^2)	Ta/T1/CIS DFR (I^2)
3 months	44% (36%) n = 4	73% (0%) n = 3	48% (46%) n = 2
6 months	38% (58%) n = 3	58% (26%) n = 5	22% (63%) n = 3
12 months	25% (77%) n = 6	48% (49%) n = 6	43% (84%) n = 3
18 months	26% (88%) n = 2	50% (0%) n = 3	–
24 months	32% (95%) n = 2	40% (65%) n = 4	–

CRR: complete response rate; RFR: recurrence-free rate; DFR: disease-free rate

and have reported CRR rates and 12-month durability that meet or exceed this bar. With the emerging data from recently completed and ongoing clinical trials, the CRR and durability threshold required for approval, particularly for patients with CIS, remains a moving target. If one or more new drugs receive FDA approval, this will provide clarity around these endpoints.

Limitations of our study include a relatively low sample size of studies using a variety of different treatment agents. Additionally, variability in study protocols allowing for therapeutic re-induction following initial non-response and/or mandating post-therapy random bladder biopsy may affect response rates seen. Lastly, it is difficult to determine whether adjudication between CIS±Ta/T1 and papillary-only tumors was performed by central review in all included studies. Despite the heterogeneity in the treatment agents used, we were successful in delineating a relatively narrow range of response rates at clinically relevant timepoints stratified by tumor stage to provide a frame-of-reference for emerging results from ongoing BCG-unresponsive clinical trials.

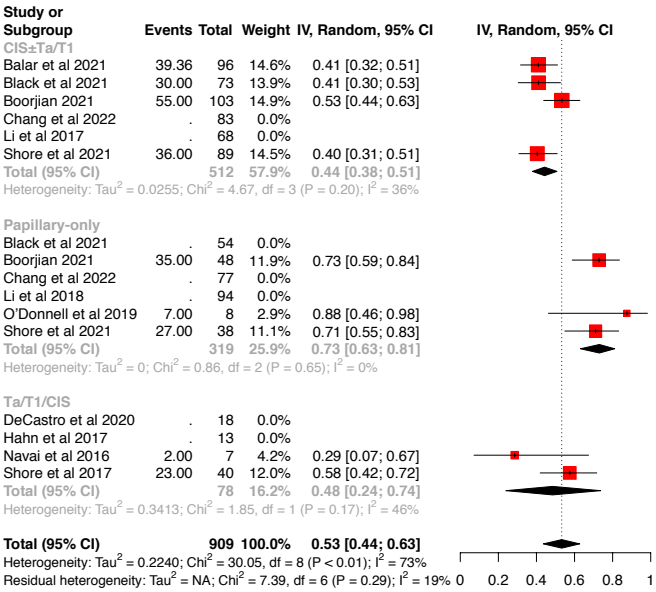
Conclusion

Our study indicates relatively uniform but disparate response rates to bladder-sparing therapies in BCG-unresponsive CIS±Ta/T1 and papillary-only NMIBC. To reduce risks of bias, randomized controlled studies with appropriate stratification of the 2 disease entities are likely to be required in the future. Consensus is also needed on the ideal therapeutic agent to be used in the control arm. Our results will help to formulate designs of future clinical trials and inform the interpretation of emerging data in this exciting treatment space.

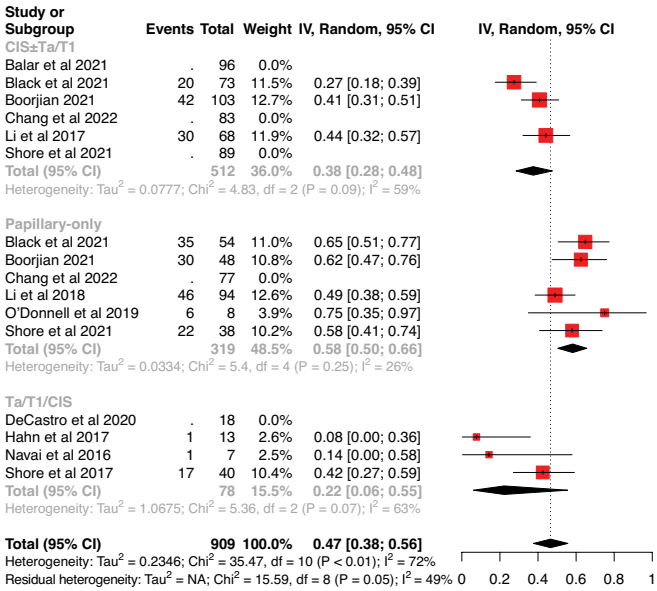
FIGURE 2.

Forest plots of response rates from meta-analysis, stratified by tumor characteristic at 3 months (A), 6 months (B), and 12 months (C)

A



B



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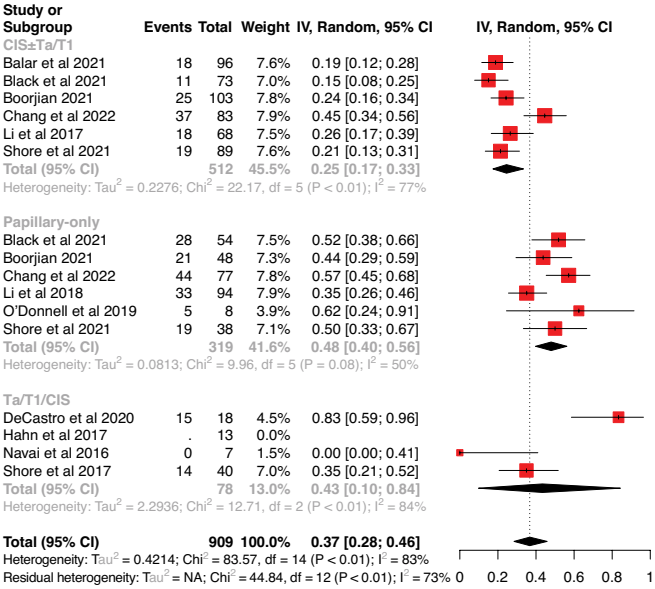
C



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