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Converging Roads to Early Bladder Cancer

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The availability of newer effective therapies in the therapeutic landscape of bladder cancer has offered intriguing opportunities to clinical investigators to improve the cure rate of patients with limited/early disease stage, while simultaneously providing new opportunities to design organ-sparing locoregional therapies to achieve cure. These advances are likely to impact the way we define the disease states, currently based on conventional diagnostic tools, and inform management, which currently relies on disappointing standard therapeutic options without validated biomarkers.

A proportion of patients with high-risk non–muscle-invasive bladder cancer (NMIBC) can be said to have clinical behavior and an underlying biology that closely resemble muscle-invasive bladder cancer (MIBC; Supplementary Table 1). Here, we aim to summarize the literature evidence and clinical trial trends in support of a more comprehensive definition of early-stage disease, which will overcome the limitations of the muscle layer involvement, resulting in broader eligibility criteria for future clinical studies.

1. The interplay between intravesical BCG-unresponsive NMIBC and early MIBC disease states

Radical cystectomy (RC) is still the recommended treatment for patients who have failed bacillus Calmette-Guérin (BCG) treatment, with its associated morbidity and long-term sequelae, serving as an inherent cause for refusal in a proportion of patients. By benefiting from the availability of a consensus definition of BCG unresponsiveness and, consequently, the possibility to harmonize the selection criteria for the post-BCG studies [1,2], a plethora of phase 1–3 clinical trials are now enrolling patients with high-grade NMIBC after failure of adequate courses of BCG therapy. Most of these studies include the use of immune-checkpoint inhibitors as the backbone therapy, either as a single agent or via combinatorial approaches, with either intravesical therapies or multiagent systemic therapies [3]. A pivotal study of systemic immunotherapy in NMIBC has been Keynote-057, an open-label, single-arm, phase 2 trial of intravenous pembrolizumab monotherapy in patients who had unresponsive NMIBC despite an adequate course of BCG and who were refusing or were unsuited for RC. The results of this study have led the US Food and Drug Administration (FDA) to accelerate the approval of pembrolizumab as a new standard therapy option for patients with carcinoma in situ (CIS) ± papillary component. In these patients, the 3-mo complete response (CR) rate was 41.2% by central assessment and the median duration of CR was 16.2 mo [4].

Like the Keynote-057 study, a plethora of other similar studies are now available for patients with similar characteristics. Of note, the interest toward the use of systemic immunotherapy in NMIBC has increased following the initial results of academic research conducted in early MIBC patients, that is, in patients with limited, clinical (c) T2-3N0M0 MIBC. In the PURE-01 study, the initial proportion of 42% pathologic CR (pT0N0) achieved in 50 patients (close to the proportion of clinical CR reported in Keynote-057) was substantially confirmed in the subsequent update,

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reporting a pT0N0 rate of 37% among 114 patients, with initial activity reported in patients with predominant squamous-cell or lymphoepithelioma-like histology [5,6].

Results from the ABACUS study (two courses of atezolizumab before RC in cT2-4N0M0 MIBC patients) recapitulated the clinical findings from PURE-01, with an overall pT0 rate of 31% (27/88 patients) [7]. Both these studies predominantly enrolled early-stage tumors (cT2), and the most promising results in terms of pT0N0 responses have been reported in this subset.

Similar to in PURE-01 and ABACUS, in the NABUCCO study (NCT03387761) patients with programmed cell-death ligand-1 (PD-L1)-expressing tumors benefited the most from the ipilimumab, nivolumab-ipilimumab, and nivolumab sequence, although the degree of significance varied across studies [8].

Supplementary Table 2 shows the opportunities that may arise from merging the available immunotherapy biomarker findings in NMIBC and MIBC. Among the most intriguing findings, analyses conducted in the PURE-01 study revealed that a contraction of tumor mutational burden (TMB) after pembrolizumab was observed in MIBC, similar to what has been observed in preliminary studies in NMIBC following BCG failure [9,10]. Despite a mechanistic lack of proof for this phenomenon (it may partly be related to immune editing, an adaptive process boosted by the early administration of immunotherapy), TMB contraction may be dependent on shared mechanisms in which immunotherapy response is generated across different clinical states. In addition, boosted T-cell infiltration and immune-activation biomarkers (eg, shifting molecular subtype to more inflamed tumor, enrichment of CD8 + T cells, and PD-L1–positive cells after treatment) have been equally observed in PURE-01 and ABACUS studies in postimmunotherapy samples. Furthermore, studies of cell-free circulating tumor DNA (ctDNA) have shown promise for predicting neoadjuvant chemotherapy response in patients with MIBC, which could aid in treatment decisions [11,12]. Importantly, ctDNA has also been detected in urine and plasma samples from patients with NMIBC and associated with a high risk of disease progression [13,14]. A clinical trial has been initiated (ie, TOMBOLA study, NCT04138628) to investigate the clinical benefit of early treatment with immunotherapy in ctDNA-positive patients after RC. Future studies should investigate the potential for ctDNA-based treatment selection, monitoring, and risk stratification within the continuous spectrum of early-stage disease.

2. Shifting the systemic therapy paradigm earlier in selected patients with high-risk NMIBC

For NMIBC, there are still concerns with the use of BCG in certain populations, represented by patients who develop intolerance (defined as the development of severe side effects that prevent further BCG instillation before completing induction), those who are unwilling to receive or unfit for BCG, and, in particular, those having very high-risk NMIBC according to the European Association of Urology guideline definition [15]. The proportion of BCG-intolerant patients or those refusing BCG in the setting of high-risk NMIBC is not well established in the peer-reviewed literature (particularly short-term intolerant patients who are unable to receive an adequate BCG course). In the literature, conflicting data exist regarding the proportion of patients with high-risk NMIBC who are unable to completing a full 3-yr course of maintenance BCG therapy, whereas the proportion of those who ultimately refuse to receive BCG is unpredictable, but likely depends on the availability of effective alternative options within clinical trials. These patient categories, added to the current limitations related to the significant BCG shortage worldwide, define a further unmet medical need. Indeed, not only the post-BCG, but also the pre-BCG space will be the new achievements for clinical research, while systemic immunotherapy trials are already accruing patients (NCT03711032, NCT03528694, NCT03504163, NCT02792192, and NCT03799835).

3. Novel imaging research unifying early bladder cancer disease states

Literature data indicate that NMIBC and MIBC share the ultimate risk of pathologic upstaging to non–organ-confined disease at RC [16]. For this reason, recent studies advocated more accurate staging and treatment planning for MIBC. In particular, a consensus definition based on a multiparametric magnetic resonance imaging (mpMRI) reporting system for bladder tumors was recently proposed: Vesical Imaging Reporting and Data System (VI-RADS) criteria are now available for clinicians and investigators to expedite clinical research [17].

These criteria have similarly been applied to NMIBC in a prospective study, the primary objectives of which were, first, to evaluate the VI-RADS performance in discriminating MIBC identified at the time of the transurethral resection of the bladder tumor (TURBT), and second, to analyze the concordance between re-TURBT reports and preoperative VI-RADS score [18]. In terms of response assessment after neoadjuvant therapy, preliminary results on the possibility of discriminating the pT0 response or residual NMIBC after treatment with the use of mpMRI have been reported from the PURE-01 study [19]. Similar considerations could be made for NMIBC, for which the noninvasive response assessment during and after BCG would allow clinicians to avoid potentially unnecessary TURBT.

4. Revisiting hospital management of patients with early bladder cancer

Based on the noteworthy scientific advances in the treatment of bladder cancer, urologic surgeons and clinical oncologists, as well as administrators and supporting staff, should be well aware of the fact that to deliver top-level technologies of imaging assessment, medical and surgical treatment will require multidisciplinary departments to shorten time and distances, and make the patient's journey

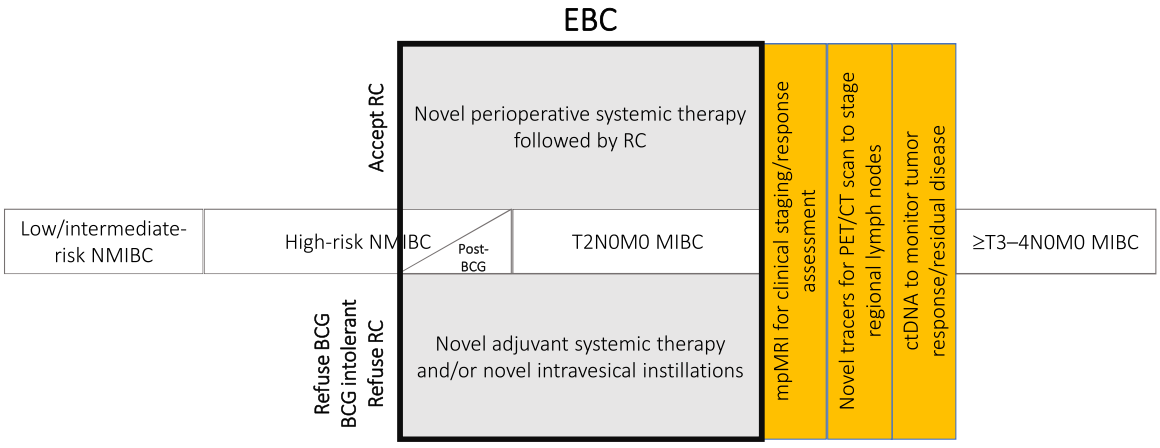

Fig. 1 – Proposed redefinition of bladder cancer clinical states following transurethral resection of the bladder tumor (TURBT) and suggested pathways of clinical research. Early bladder cancer definition includes patients represented within the thick squared box. Additional opportunities for clinical stage refinement or therapeutic response monitoring that are emerging from the literature are indicated in the yellow boxes. BCG = bacillus Calmette-Guérin; ctDNA = circulating tumor DNA; EBC = early bladder cancer; MIBC = muscle-invasive bladder cancer; mpMRI = multiparametric bladder magnetic resonance imaging; NMIBC = non–muscle-invasive bladder cancer; PET/CT = positron emission tomography/computed tomography scan; RC = radical cystectomy.

as streamlined and effortless as possible. Unfortunately, stagnant organizational processes are often inadequate to meet the tremendously rapid pace of scientific improvements and treatment changes currently defining the bladder cancer landscape. Detailed guidance to healthcare system, through the adoption of minimum consensus requirements indicated by referral organizations, is warranted. A fundamental "cultural" paradigm shift is critical in embracing these continuous changes as the new standard that we must adapt and integrate in our therapeutic armamentarium. This change is urgently required due to the need to provide a safe use of immune-checkpoint inhibitors in a multidisciplinary environment. As we reported from PURE-01, in fact, meticulous surgical safety reporting resulted in up to 34% high-grade complications following pembrolizumab and RC in a referral center [20].

5. Conclusions

The common clinical behavior, preliminary biomarker findings, and, most importantly, the availability of several clinical trials addressing early bladder cancer states support the call for a more comprehensive definition of the disease, not limited to the presence of muscle invasion. Similar to the definition adopted for breast cancer, we propose the use of early bladder cancer definition as indicated in Fig. 1, including selected high-risk NMIBC and limited-stage MIBC. Use of this clinical state would help broaden the inclusion criteria of next-generation clinical trials testing novel systemic therapies either in the preoperative setting or as adjuvant therapies following a conservative approach. The latter approach would equally benefit from the use of novel emerging intravesical therapies in a broader population of patients similar to those shown in Fig. 1. Moreover, the early bladder cancer state would help redefine the unmet need, and the ongoing evolution of tumor and radiologic biomarker discovery and validation efforts across this single disease state.

Conflicts of interest: A. Necchi: https://coi.asco.org/share/GVM-M7NL/Andrea%20Necchi. P. Grivas: https://coi.asco.org/share/AM6-Y2LD/Petros%20Grivas. M. Roupret: advisory role for MSD, Roche, Astra Zeneca, Arquer, Cepheid, and Nucleix. P.E. Spiess: member of the NCCN Bladder and Penile Cancer Panel. A.M. Kamat: grants or funding—BMS, CEC Oncology, FKD, Merck, and Photo Cure; consultancies—Abbott Molecular, Arquer, Asieris, Astra Zeneca, BioClin Therapeutics, BMS, Cepheid, Cold Genesys, Eisai, Ferring, IBCG, MDx Health, Medac, Merck, Pfizer, Photocure, Roviant, Theralase, and US Biotest; royalties or patents—CyPRIT (Cytokine Predictors of Response to Intravesical Therapy), joint with UT Anderson Cancer Center; president—International Bladder Cancer Network (IBCN) and International Bladder Cancer Group (IBCG). E.A. Gibb: Employee of Decipher Biosciences, Inc. L. Dyrskjøt: consultant for Ferring; grant/research support from Ferring and Natera. A. Gallina, A. Briganti, and F. Montorsi: nothing to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.02.031.

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