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Editorial

Regional Node–positive Bladder Cancer: Therapeutic Decisions Based on Trial Results in Perioperative and Advanced Disease Settings

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Locally advanced bladder cancer includes cases with extravesical tumor (cT3/T4) and/or regional lymph node (LN) involvement (cN+) [1]. Regional nodal staging distinguishes cN1 versus cN2–3, and the heterogeneity of node-positive disease means that individualized strategies are required [1]. In the absence of level 1 evidence from dedicated phase 3 trials in patients with stage cN+ M0 bladder cancer, multicenter retrospective analyses have explored multimodal treatment approaches that combine systemic induction chemotherapy and subsequent consolidation with local therapy. Pathologic complete response (pCR) rates reported for cN+ patients are lower than in cN0 cohorts, reaching up to 19% [2,3] and reflects heterogeneity in nodal status, chemotherapy regimens, and the number of treatment cycles [2–4]. Despite modest primary-tumor responses, up to 60% of patients with cN+ stage may achieve ypN0 status after induction chemotherapy, which was associated with longer survival [2–4]. The best outcomes have been observed for patients who received cisplatin-based chemotherapy, had negative surgical margins, and achieved ypN0 status after radical cystectomy (RC) [4]. In the CLIPOLY study, the 2-yr overall survival (OS) rate was 63% after induction chemotherapy followed by consolidative RC for patients with cTany N+ M0 stage [3]. However, Necchi et al. [5] found no significant OS benefit from LN dissection (LND) after induction chemotherapy for patients with pelvic or retroperitoneal LN involvement, regardless of chemotherapy response. Nevertheless, the 36-mo OS improvement was 10.6% for patients with cN+ disease treated with chemotherapy + LND (51.7% vs 41.1% with chemotherapy alone) [5], consistent with CLIPOLY results (3-yr OS 55%) [3].

In stage cN0/N1 disease, perioperative systemic therapy before or after RC represents the new standard of care in fit patients with cT2–4a muscle-invasive bladder cancer (MIBC) without distant metastases (M0). Two phase 3 trials demonstrated significant improvements in event-free survival, OS, and the pCR rate [6,7]. For cisplatin-eligible patients, gemcitabine + cisplatin (GC) plus perioperative durvalumab significantly outperformed neoadjuvant GC alone followed by RC [6]. For cisplatin-unfit patients, perioperative enfortumab vedotin + pembrolizumab (EV/P) was associated with notably superior outcomes in comparison to RC alone [7]. Both trials included a small number of patients with a single enlarged pelvic lymph node (cN1 M0; NIAGARA 58/1063, 5.5% [6]; EV-303 17/344, 4.9% [7]), which suggests a benefit in these patients, who are usually managed similarly to individuals with cN0 M0 disease. Ongoing phase 3 trials, including KEYNOTE B-15/EV-304 (NCT04700124, with a press release reporting a survival benefit with perioperative EV/P in cisplatin-fit patients), KEYNOTE-866 (NCT03924856), ENERGIZE (NCT03661320), and VOLGA (NCT04960709) have enrolled patients with cN0/N1 MIBC. Thus, the optimal therapeutic management of cN1 disease consists of perioperative systemic therapy combined with RC (Fig. 1).

In cN2-3M0 disease—defined as metastases in multiple regional LNs within the true pelvis, including the hypogastric, obturator, external iliac, or presacral nodes (cN2), and

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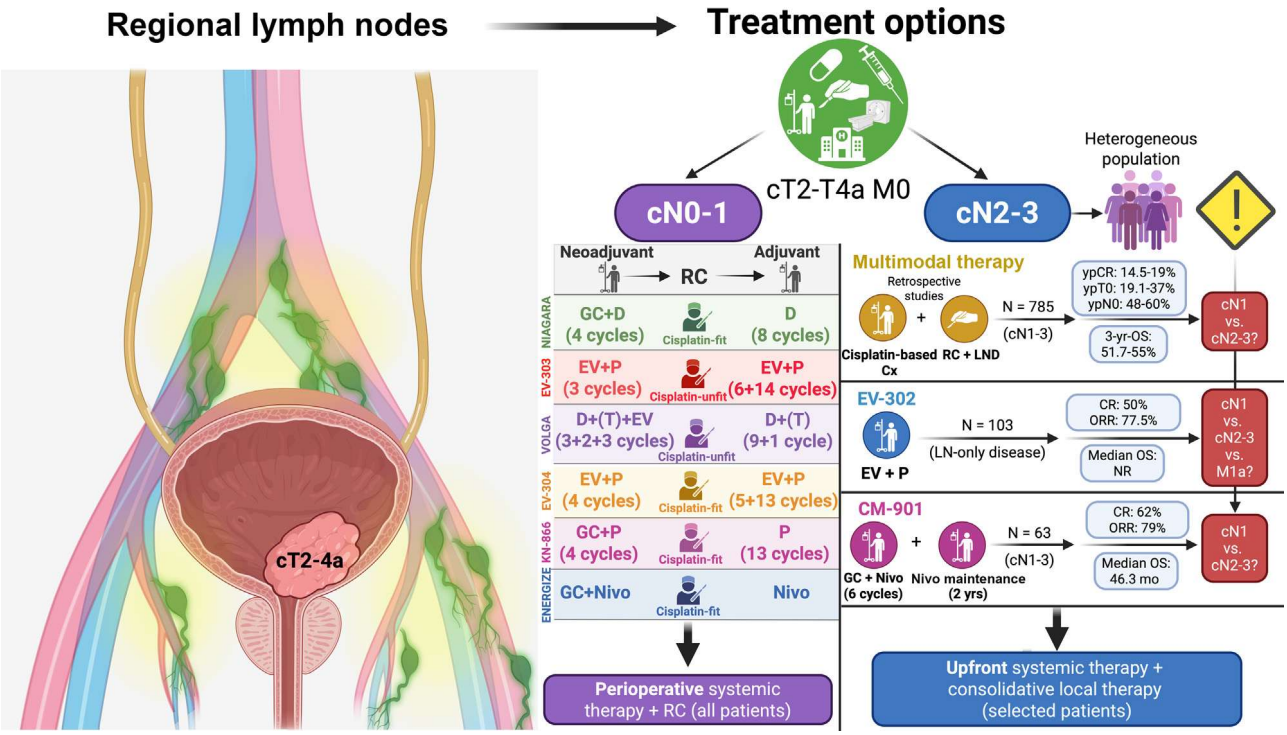

Fig. 1 – Graphical overview of potential therapeutic strategies according to the clinical status of regional lymph nodes (cN0–1 vs cN2–3) in bladder cancer. While perioperative systemic therapy before or after radical cystectomy in the cN0–1 M0 setting is the standard of care for all patients (cisplatin-fit: neoadjuvant GC + perioperative durvalumab; cisplatin-unfit: perioperative EV/P) in various ongoing phase 3 trials (NCT04700124, KEYNOTE-866, NCT03924856, NCT03661320, NCT04960709), the therapeutic landscape for patients with locally LN-advanced stage (cN2–3 M0) depends on advanced stage trials and retrospective studies, in which such patients represent a highly heterogeneous population. A multimodal treatment approach consisting of induction systemic therapy followed by RC may achieve pCR and ypN0 rates of 14–19% and 48–60%, respectively [4–6]. However, retrospective studies may not have adequate breakdown of data between cN1 and cN2–3 stages. The CM-901 [9] and EV-302 [8] trials included approximately 12.2% and 5.1% of patients, respectively, with unresectable locally advanced M0 disease. A post hoc analysis of the CM-901 trial included 63 patients with isolated cN+ disease. The CR rate was 62% (ORR 79%), and median OS reached 46.3 mo [10]. In EV-302, median progression-free survival and OS were not reached in the group of patients with LN-only disease [8]. However, these trials did not perform a dedicated powered subgroup analysis specifically for cN2–3 M0 stage, which represents a heterogeneous population. RC = radical cystectomy; CR = complete response; pCR = pathological complete response; ORR = objective response rate; NR = not reached; GC = gemcitabine + cisplatin; D = durvalumab; EV = enfortumab vedotin; P = pembrolizumab; Nivo = nivolumab; T = tremelimumab; Cx = chemotherapy; LN = lymph node; LND = LN dissection; OS = overall survival.

metastases in the common iliac LNs (cN3) [1]—optimal management relies on data from trials that enrolled patients with locally advanced/metastatic stage and retrospective studies (Fig. 1). Given that patients with cN2–3 stage represented only a small subgroup in retrospective cN+ cohorts [2,3] and that the pCR rate to induction chemotherapy at the time of RC (pN0: 39% vs 56%) and OS (median 17 vs. 24 mo) were inferior in comparison to the cN1 setting [2], the notion remains that patients with cN2–3 M0 disease should be managed primarily with novel first-line combinations such as EV/P (preferred) [8] or GC + nivolumab [9] that are also approved for locally advanced (unresectable) disease. Both the EV-302 [8] and CheckMate 901 [9] trials included relatively small subsets of patients with unresectable locally advanced (cT4b and/or cN+) M0 disease (EV-302 45/886, 5.1%; CM-901 74/608, 12.2%). In both trials, patients with LN-only disease (cN+ and/or M1a) derived the greatest degree of benefit. In LN-only disease, the objective response rate (ORR) ranged from 77.5% [8] to 81% [9], with CR rates of 50% and 63% for EV/P and GC + nivolumab, respectively [8–10]. However, in EV-302, the LN-only subgroup was not stratified into pelvic (cN1 and cN2–3) versus retroperitoneal/distant LN metastases (M1a), which resulted in a heterogeneous population for this category [8]. An exploratory analysis of CheckMate 901 revealed that among patients with cN1–3 disease (n = 63), GC + nivolumab was superior to GC alone (CR: 62% vs 17%; ORR: 79% vs 52%). Median OS reached 46.3 mo, with rapid CR achievement (median 2.1 mo) and prolonged CR duration in comparison to chemotherapy alone (median 37.1 vs 13.2 mo). By contrast, the subgroups with positive retroperitoneal/distant LNs (M1a) showed smaller differences (retroperitoneal: 77% vs 74%; distant: 80% vs 67%) [10]. However, the CheckMate 901 data set does not specify the distribution of cN1 versus cN2–3 cases within the pelvic subgroup, and the role of potential locoregional consolidative strategy after systemic therapy remains unclear. Details regarding the proportion of patients with residual primary tumor versus isolated nodal disease were not provided [10]. Moreover, pCR rates after chemotherapy and RC + LND in retrospective studies [2–4] cannot be directly compared to clinical CR rates in the CM-901 or EV-302 trials [9,10], as the latter refer exclusively to radiologic response and not pathologic examination. A retrospective analysis

indicated that consolidative surgery following induction EV/P appeared to be feasible and was associated with encouraging early oncologic outcomes in well-selected patients with advanced disease (pCR 43%, with 82% of patients experiencing pathologic downstaging of the primary tumor) [11]. Validation to support the potential role of surgical consolidation in patients with a deep or durable response to modern systemic therapies is needed, as treatment de-escalation and thus a reduction in the toxicity burden may be an option for these patients.

Conflicts of interest: Petros Grivas reports consulting roles for MSD, Bristol-Myers Squibb, AstraZeneca, EMD Serono, Pfizer, Janssen, Roche, Astellas Pharma, Gilead Sciences, Strata Oncology AbbVie, Bicycle Therapeutics, Replimune, Daiichi Sankyo, Foundation Medicine, Eli Lilly, Urogen, Tyra Biosciences, and Natera; and institutional research funding from Bristol-Myers Squibb, MSD, EMD Serono, Gilead Sciences, Acrivon Therapeutics, ALX Oncology, and Genentech. Renate Pichler reports research funding from Ipsen, AstraZeneca and Astellas Pharma; and consulting roles for MSD, Merck, Ipsen, Janssen, Astellas Pharma, AstraZeneca, Pfizer, and Recordati. The remaining authors have nothing to disclose.

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