Is there a role for maintenance therapy after platinum chemotherapy in bladder cancer in the era of immune therapy?

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“The ICI maintenance strategy paradigm increases exposure to effective therapies especially through a switching approach in patients who achieve disease control after front-line chemotherapy”

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Urothelial bladder carcinoma (UC) is the fourth most common cancer diagnosed among men and the second urological malignancy after prostate cancer [1,2]. Metastatic disease occurs in 50% of patients with muscle-invasive tumors despite systemic therapies and 10–15% of patients at initial presentation [3]. The management of patients at the metastatic stage depends on a consensus statement of cisplatin-eligibility where the following criteria should be avoided: PS > 1, stage III chronic kidney disease, grade ≥ 2 audiometric loss, peripheral neuropathy and New York Heart Association class III heart failure [4]. Patients within this category are treated with cisplatin-containing combination chemotherapy, which has been the standard of care since the late 1980s demonstrating an overall survival (OS) of 12–14 months in different series [5]. Immune checkpoint inhibitors (ICI) have shown significant antitumor activity and durable responses in pretreated patients with metastatic UC [6,7]. Subsequently, ICI got approved in the front-line treatment of unfit patients with PDL-1 positive expression and in the second-line treatment of patients pretreated with a platinum-based chemotherapy. Maintenance therapy after clinical benefit from platinum-based therapy was recently evaluated by switch chemotherapy or targeted therapy or even ICI. The main goal of this strategy is to reduce or postpone disease relapse in patients who benefited from first-line chemotherapy with prevention of symptoms worsening by using effective and safe drugs. Maintenance therapy demonstrated promising outcomes in certain types of solid tumors such as ovarian, lung and colorectal cancer but is not yet considered a standard of care in UCs [8–11]. In this paper, we opted to evaluate the role of maintenance strategy in metastatic urothelial carcinoma (mUC) in order to understand the optimal sequence of treatment administration.

Switch maintenance

The maintenance therapy with conventional and targeted agents did not significantly impact the oncological outcomes of patients with metastatic UC [12]. Three prospective randomized controlled trials have been published in this regard. The first trial is a Phase II multicentric study (MAJA; SOGUG 2011/02) that randomized 88 patients with mUC who had disease control after 4–6 cycles of platinum-based chemotherapy with gemcitabine to receive vinflunine (280–320 mg/sqm every 3 weeks; 45 pts) or best supportive care (43 pts). Vinflunine, a vinca-alcaloid antineoplastic agent that targets microtubules, is approved by the European Medicines agency in the relapsed setting of mUC after demonstrating significant improvement in progression-free survival (PFS), overall response rate but not in OS in the intention-to treat population [13]. The experimental arm demonstrated PFS (6.2 vs 4 months [HR = 0.59, 95% CI: 0.37–0.96]) and OS (16.7 vs 13.2 months) benefit. The overall response rate was also in favor of the experimental arm (21 vs 7%) but with more common gr. 3–4 side effects with vinflunine neutropenia (18% vs 0), fatigue (16 vs 2%) and constipation (14% vs 0). In a post-hoc multivariate analysis including all stratification

factors, only vinflunine therapy and liver metastasis were associated with prolonged PFS [14]. The second trial used the same study design and randomized patients with advanced mUC who had disease control after 4–6 cycles of chemotherapy to maintenance therapy with sunitinib (50 mg dose daily for 28 days on a cycle of 6 weeks) (26 pts), an anti-angiogenic tyrosine kinase inhibitor or placebo (28 pts). The median PFS (2.9 vs 2.7 months, [HR = 1, 95% CI: 0.6–1.8]) and OS [10.5 vs 10.3 months]) were not statistically different between the two arms but the study was terminated earlier due to slow accrual [15]. Grade 3–4 adverse events in the sunitinib group were thrombocytopenia (30.8%), fatigue (19.2%), diarrhea and mucositis (15.4%) and hypertension (11.4%). The third is a Phase III trial that enrolled patients with HER1-HER2 positive (3+ on immunohistochemistry) mUC who had disease control after 4–8 cycles of platinum-based chemotherapy to receive lapatinib (1500 mg daily; 116 pts) or placebo (116 pts). The median PFS (4.5 vs 5.1 months, [HR = 1.07, 95% CI: 0.81–1.43]) and OS (12.6 vs 12 months, [HR = 0.96, 95% CI: 0.70–1.31]) were not statistically different in the two arms [16].

The preclinical scientific rationale for ICI maintenance following chemotherapy is intriguing although not clearly documented. Carcinogenesis occurs in an evolving immune environment where the immune system initially eliminate tumors cells who develop immunosuppressive properties leading to immune escape and ultimately disease progression [17]. Chemotherapy exerts immunomodulatory changes that impacts regulatory T cells and myeloid-derived suppressor cell. The effects of chemotherapy vary with the specific agents and doses administered [18]. The relevant drugs in bladder cancer namely gemcitabine and platinum agents are immunosuppressive thus can deplete regulatory T cells and increase T-cell proliferation and natural killer cell lytic activity [19,20]. PD-L1-targeted approaches can overcome immune-evasion mechanisms elicited by chemotherapy and augment immune-mediated tumor control.

In this regard, the Phase II double-blind randomized controlled trial (NCT02500121) has assessed the role of ICI maintenance in mUC [21]. The study randomized 107 patients with metastatic UC who achieve stable disease following ≤ 8 cycles of platinum-based regimen to maintenance pembrolizumab (200 mg intravenously [iv.] every 3 weeks; 55 pts) or placebo (52 pts) for a total of 24 months followed by observation until recurrence. The crossover to pembrolizumab in case of disease progression under placebo was permitted. The pembrolizumab arm achieved longer PFS (5.4 vs 3.2 months, [HR = 0.64, 95% CI: 0.41–0.98]) and 18-month restricted mean PFS (8.1 vs 5.5 months; $p = 0.023$). It also showed higher overall response (22 vs 12%) and disease control rate (57 and 41%). Overall, grade 3–4 adverse events were reported in 53% with ICI and 35% with placebo. The most common side effects reported being fatigue (7 vs 0%), increased liver enzymes (5 vs 0%) and dyspnea (5 vs 0%) [21]. Another ongoing trial in this regard is the JAVELIN Bladder 100 study (NCT02603432) is evaluating maintenance avelumab in patients with advanced UC who have completed at least four cycles of platinum-based chemotherapy without evidence of disease progression.

Continuous maintenance

With the introduction of ICIs at earlier stages in the management of mUC, the role of maintenance therapy has been put into question. Recently, an announcement has confirmed that the addition of atezolizumab to platinum-based regimen in the first-line setting of LA- or mUC-improved PFS in the Phase III trial (IMvigor130). In this trial, patients with LA or mUC were randomized to receive atezolizumab (1200 mg iv. every 3 weeks) alone, in combination to chemotherapy (gemcitabine 1000 mg/sqm d1 and d8 with carboplatin area under the curve 4.5 d1 or Cisplatin 70 mg/sqm d1 every 3 weeks) or chemotherapy alone [22]. With the addition of ICIs at earlier stages of the disease, the role of switch-maintenance is questionable, whereas future trials should assess the role of continuous maintenance ICIs in those exhibiting response after first-line immunotherapy.

Conclusion

The ICI maintenance strategy paradigm increases exposure to effective therapies especially through a switching approach in patients who achieve disease control after front-line chemotherapy. Usually, a high percentage of patients progressing after the first line of chemotherapy never receive second-line therapy at the time of progression. The maintenance strategy ensures that the majority of patients receive ICI, which have proven efficacy and durable response in mUC. The available biological and clinical data support this hypothesis and required further validation in Phase III trials. Questions concerning the efficacy of this strategy remain unanswered.

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