

## MULTIPLE COMBINATIONAL STRATEGIES OF IMMUNOTHERAPY FOR UROTHELIAL CARCINOMA IN ONE INSTITUTION

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**Background** Urothelial cancers are immunogenic and may benefit from anti-PD1/PDL1 no matter in front-line cisplatin-ineligible patients (IMvigor210) or 2nd line setting (KN45). Avelumab maintenance after 1st line platinum-based chemotherapy (JAVELIN Bladder 100) in 1st line setting has offered survival benefits. Antibody drug conjugates (like enfortumab vedotin and sacituzumab govitecan) have shown encouraging efficacy in later lines and tried to be combined with anti-PD1/PDL1 in front-line setting. Furthermore, in the era of precision medicine, FGFR inhibitors, HER2 targeting agents, and PARP inhibitors may be introduced to urothelial cancers alone or in combination with anti-PD1/PDL1. Although lenvatinib combined with pembrolizumab (LEAP11) had failed to get survival benefit compared with chemotherapy in frontline setting, cabozantinib is used for (1) maintenance therapy alone or with avelumab after 1st line chemotherapy; (2) combination with atezolizumab for later line treatment.

**Methods** From early 2016 to 2022, 55 advanced urothelial cancers patients had ever received immunotherapy-containing regimens in Yun-lin Branch of National Taiwan University Hospital. We have reviewed basic characteristics and therapeutic regimens of these patients to find out treatment outcomes of combinational strategies of immunotherapy and special characters of responders.

**Results** Immunotherapy-based combinations have brought objective response rates in 73% (40/55) and clinical benefits in 91% (50/55). Front-line Gemcitabine (11) or Taxane (7) and cisplatin with bevacizumab and atezolizumab (12) or pembrolizumab (6) were administered to 18 patients and 94% objective response rate was got. In one of these patients, HER2 amplification was noted by NGS analysis and atezolizumab with Herceptin & afatinib maintenance was given thereafter. Only 5/55 (9%) of the total patients had received NGS studies (No FGFR derangements seen, 1 HER2 amplification, 2 BRCA2 mutation). Olaparib was not given for these 2 BRCA2 mutation patients. 12 patients with ureter cancers received 2nd line immunotherapy combinations (Pembrolizumab 9, Nivolumab 1, Nivolumab with CT 1, low dose nivolumab 20 mg per 2 weeks with metronomic cyclophosphamide 1) and objective response rate was 58% (7/12). 18 patients with ureter cancers (Avastin 200 mg per 3 weeks, Atezolizumab, & CT in 13; Avastin, Pembrolizumab, & CT in 2; low dose nivolumab with metronomic cyclophosphamide 3) received front-line immunotherapy-containing regimens and objective response rate was 94%. 7 patients with single kidney received neoadjuvant atezolizumab monotherapy (5) or low dose nivolumab with metronomic cyclophosphamide (2) and objective response rate was 57% (4/7) with clinical benefits in 100%. Total 30 patients with ureter cancers have received immunotherapy-based combinations and 80% (24/30) ORR was got. Low dose nivolumab with metronomic cyclophosphamide was administered in 4 ureter cancers (1 2nd line, 3 1st line, 2 cisplatin-ineligible) and the response rate was 75% with 100% clinical benefits. No avelumab maintenance was given in our series.

**Conclusions** In Taiwan, urothelial cancers are still a health burden due to smoking and aristolochic acid in Chinese

medicines. In our institution, bevacizumab and anti-PD1/PDL1 with platinum-based chemotherapy has shown encouraging efficacy in nearly all UC patients, esp. for high tumor burden with rapid progression, and may be a potentially front-line treatment in the future deserving further clinical trial development focusing on bevacizumab and atezolizumab maintenance. Most ureter cancers have responded to immunotherapy-containing regimens, esp. in front-line combinations. Metronomic dose cyclophosphamide (suppress Treg) with low dose nivolumab could be an exciting regimen for CT-unfit or cisplatin-ineligible patients with economic concerns.

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.0805>