Nectin-4 inhibitors: An ace up our sleeve against advanced urothelial carcinoma

Santosh Kumaraswamy
Department of Urology, AIIMS, Bhubaneswar, Odisha, India
*E-mail: urol_swaranndu@aiimsbhubaneswar.edu.in, santosh3091@gmail.com

SUMMARY

Enfortumab vedotin (EV)-301,[1] a phase three trial, evaluated EV for treating patients with locally advanced or metastatic urothelial carcinoma who had previously received platinum-based chemotherapy and progressed during/after second-line therapy with PD-1 or PD-L1 inhibitors. Eligible candidates were randomized 1:1 to receive either EV as 28-day cycles (1.25 mg/kg on days 1, 2, and 15) or physician choice second-line chemotherapy (paclitaxel, docetaxel, or vinflunine). The primary endpoint was overall survival (OS). Principal secondary endpoints included progression-free survival (PFS), clinical response (RECIST 1.1), and safety profile. Six hundred-eighty candidates were randomized at 191 centers across 19 countries to receive EV (301 patients) or chemotherapy (307 patients).

The median OS was 12.88 months (95% confidence interval [CI], 10.58–15.21) in the EV group and 8.97 months (95% CI, 8.05–10.74) in the chemotherapy group. At a median follow-up of 11.1 months, the risk of death was 30% lower with EV than with chemotherapy (hazard ratio, 0.70; 95% CI, 0.65–0.89; P = 0.001). OS benefit was better with EV in a subgroup analysis, irrespective of age, performance status, liver metastasis, primary site of the tumor (upper tract vs. bladder), number of previous systemic therapies, and response to previous immune checkpoint inhibition (ICI). With a median PFS of 5.55 months (95% CI, 5.32–5.82), there was a 38% lower risk of progression or death (hazard ratio, 0.62; 95% CI, 0.52–0.75; P < 0.001) in the EV group against a median PFS of 3.71 months (95% CI, 3.52–3.94) in the chemotherapy group. Overall response (complete or partial) was higher with EV than chemotherapy (40.6% [95% CI, 34.9–46.5] vs. 17.9% [95% CI, 13.7–22.8]; P < 0.001). Likewise, disease control (complete/partial response and stable disease) was also better with EV (71.9% [95% CI, 66.3–77.0] vs. 53.4% [95% CI, 47.5–59.2]; P < 0.001).

Overall treatment-related adverse events were very high but with similar incidence rates in both the groups (93.9% with EV and 91.8% with chemotherapy). Nearly half of all the patients in both groups reported a grade 3 or higher adverse events. Skin rashes (43.9%), peripheral sensory neuropathy (46.3%), and hyperglycemia (6.4%) were notable and frequent adverse events of particular interest with EV. Peripheral neuropathy was the leading cause of dose reduction, interruption of treatment, or withdrawal of treatment.

CRITICAL ANALYSIS

Platinum-based chemotherapy is the first-line therapy for advanced and metastatic urothelial carcinomas, of which about 50% progress. Immunotherapy with PD-1 and PD-L1 inhibitors is a standard second-line therapy with only a 15%–20% response rate. Although recent trials have shown that maintenance immunotherapy following induction chemotherapy might improve OS, many patients have disease progression.[2] An available genetics-driven option targets FGFR2/3 mutation using a fibroblast growth factor inhibitor – erdafitinib (8 mg/day). BCL2001, a phase 2 trial, showed an excellent objective response rate of 40%.[3] However, a bottleneck in such a therapeutic plan is the low expression of FGFR2/3 mutations (20%) in advanced urothelial tumors.

Nectin-4 is a transmembrane cell adhesion molecule abundantly expressed in bladder tumors and is known to activate the AKT pathway facilitating cellular proliferation. EV, a first of its class antibody-drug conjugate, is a human monoclonal antibody against nectin-4, conjugated with monomethyl auristatin E (MEME). MEME binds to the tubules and disrupts the microtubule network. Conjugating MEME with an antibody limits its toxicity to only those cells expressing the corresponding antigen. EV showed excellent tumor response rates with manageable toxicity in the phase 2 EV-201 trial, following which the US Food and Drug Administration granted it an accelerated approval.[4]

The EV-301 trial was a well-designed randomized controlled trial to evaluate the benefits of EV. The key points to note were an OS benefit of 3 months and PFS benefit of 1.84 months with EV compared to conventional chemotherapy along with a 30% reduction in the risk of death at a follow-up of 11.1 months. This advantage was seen irrespective of the metastatic burden, previous choice of chemotherapy, and the response to previous ICI.
Although the results were statistically significant, the actual clinical benefit is limited. It is interesting to note that the study did not require nectin-4 estimation for inclusion of participants as the receptor is universally overexpressed in urothelial tumors. The study was stopped after the first interim analysis as it met the primary endpoints. The authors reported that adverse events were mild to moderate which were managed easily. However, an extremely high overall adverse event rate of 93.9% with a grade 3 or higher event was seen in half of the participants. This resulted in drug discontinuation in 14% of the participants, the most common reason being neuropathy.

Management of metastatic urothelial carcinoma is evolving constantly. Initial cisplatin-based chemotherapy with avelumab has become the standard of care recently. The present study consolidates the role of nectin-4 inhibitors in patients progressing on ICI, thus providing clarification on the appropriate sequencing of these drugs. Further studies evaluating a combination of EV with immunotherapy are ongoing,[5] the results of which are eagerly awaited and may push it as a first-line treatment (ClinicalTrials.gov-NCT04223856, NCT03288545, NCT03924895). EV is undoubtedly a new ace up our sleeve, diversifying the available treatment options. However, the lack of universal availability presently in India is an issue. Furthermore, the high cost of treatment (~$3000/30 mg vial) might tax the common man’s pocket, hindering its early adoption in India.

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