New Salvage Treatments for Metastatic Bladder Cancer

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Patients with metastatic (M1) Urothelial cancer (UC) have an extremely ominous prognosis, with a 5 year survival rate of <5% after receiving cisplatin-based combination chemotherapy [1–3]. Thus, it is highly welcome news that within a year, two publications of Phase II (or I–II) trials of novel agents, erdafitinib [4] and enfortumab vedotin (EV) [5], have reported their efficacy and toxicity in patients with previously treated metastatic or unresectable UC. Each report impressive and similar objective response rates (ORRs) including complete responses (CRs) and prolongation of survival in several groups of patients. These are the most impressive additions to the armamentarium to combat metastatic UC since reports of checkpoint inhibitors (CPIs). Importantly both erdafitinib and EV are similarly effective in patients who have received and progressed on CPIs as in those who have not received CPIs.

Erdafitinib is an oral tyrosine kinase inhibitor of types 1–4 fibroblast growth factor receptor (FGFR 1–4) and has been tested primarily in patients whose tumors have FGFR 2 and/or FGFR 3 alterations (mutations and fusions). These are particularly common in patients who do not respond to CPIs [6]. Approximately 20% of patients with advanced UC have FGFR alterations [7] and these are more common (37%) in patients with upper tract UC [8]. Loriot and colleagues reported results of what was essentially a randomized phase II study of patients with metastatic UC who had progressed on first and often second line systemic chemotherapy and at times CPIs [4]. Participants took erdafitinib on an intermittent (7 days “on” and 7 days “off”) vs. a continuous schedule. Partway into the study, because they found no reduced toxicity with intermittent dosing, the investigators converted all patients to the continuous regimen of 8 to 9 mg daily. The major toxicities were hyperphosphatemia (a natural response to FGFR inhibition), stomatitis, diarrhea, decreased appetite, fatigue, anemia, and hyponatremia. Most of these side effects were controlled with reduced dosing and supportive therapy. Overall 46% of patients experienced Grade 3 toxicities – usually managed by dose reduction, but 13% discontinued treatment because of adverse events (none fatal). Overall 40% of patients experienced ORs (CRs in 3%), and ORs were higher (59%) in those who received prior CPI treatment. Median duration of progression free survival (PFS) was 5.5 months and of overall survival (OS) was 13.8 months. This agent was not tested in patients without FGFR alterations.

As opposed to erdafitinib, whose target is only found in a minority of advanced UCs, EV’s target, Nectin -4, a trans-membrane immunoglobulin-like protein implicated in cell-cell adhesion [9], and in processes such as immune modulation and host pathogen interactions [9], is expressed by almost all advanced UCs [5, 9]. Nectin -4 also has moderate expression in human skin [10–13]. EV is an intravenously administered humanized antibody to Nectin -4 drug conjugate that delivers a micro-tubular dis-
rupting agent, Monomethyl Auristatin E (MMAE) to cells expressing Nectin -4 [5, 10]. As it turns out, Nectin -4 is so frequently expressed in advanced UC that the investigators felt further testing for Nectin -4 expression was not needed for UC (while it was for other cancers) [5]. In a phase I and Phase II combination trial [5] of similarly heavily pretreated patients with metastatic UC as were studied with erdafitinib (see above), patients received 0.5, 0.75, 1.0 or 1.25 mg/kg IV infusions of EV on days 1, 8 and 15 of a 28 day cycle. 1.25 mg/kg was selected as the maximum dose because the need for dose lowering due to toxicity reached 35% in this group [5]. Major toxicities included rash (due to Nectin -4 expression in normal skin), diarrhea, and neuropathy (due to MMAE’s microtubule effect) usually managed by dose reduction or missing an infusion. Grade ≥ 3 toxicities were very uncommon below a 1.25 mg/kg dose of EV.

Objective responses were seen in 43% of patients (with 5% CRs). The median response duration was 7.4 months. Median PFS was 6 months and OS 12.3 months. Importantly as with erdafitinib, neither gender, age (≥75 or <75 years) nor site of metastasis significantly affected results. However, unlike erdafitinib where prior CPI treatment predicted a better ORR, prior CPI treatment did not influence OR to EV.

While by no means a home run, these reports of fairly small Phase II studies (N = 99 for 8–9 mg daily erdafitinib and N = 112 for 1.25 mg/kg EV), provide extremely welcome news for patients with advanced UC, their families, and their treating oncologists. Indeed, along with cisplatin-based combination chemotherapy and CPIs (including alone or in combination with themselves or chemotherapy), these reports may provide a glimmer of hope that advanced UC could become a “chronic” disease like some other malignancies now are.

CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

REFERENCES