Therapy Attrition and Lessons for Future Approaches to Treatment of Advanced Urothelial Cancer

Metastatic or advanced urothelial cancer (aUC) is an aggressive disease, and many patients with this malignant neoplasm do not survive past their first line of therapy. The study by Thomas et al is important in highlighting the significant rates of therapy attrition that still exist for patients with aUC, even in the context of multiple recent drug approvals and significant recent advances in the treatment landscape of this disease. This retrospective cohort study evaluated 7260 patients across approximately 280 oncology practices in the US between 2011 and 2023. The study found that slightly more than one-third of all patients (2714 [37.4%]) who started first-line therapy for aUC received second-line treatment, while far fewer patients (857 [11.8%]) received third-line treatment. These numbers, while striking, are consistent with previously reported data from large databases of patients with aUC, although this study included patients from the most recent period ending in 2023. It is also notable that many of the first-line regimens that patients received in this analysis were carboplatin-based therapies or monotherapy regimens with immune checkpoint inhibitors. Many oncologists specializing in urothelial cancer would now consider these treatment approaches to be suboptimal for this disease in the first-line setting, given the recent advances in this space.

The last 5 to 10 years have witnessed significant changes in the treatment of patients with aUC. Recent drug approvals and ongoing clinical trials continue to make this a dynamic treatment space. In 2023, platinum-based chemotherapy, which has long been the standard of care for first-line treatment of patients with aUC, was displaced from this role with the approval of the combination of enfortumab vedotin and pembrolizumab based on the results of EV-302 clinical trial. However, these recent developments in the academic setting take time to percolate to community practices, where most patients seek their oncology care. Given that most patients with cancer rely on community oncologists for their care and treatments, studies like this one are important to highlight therapies that most patients in the US will actually receive. These significant attrition rates are noteworthy and underscore important challenges in the care of these patients and for the field of urothelial cancer moving forward.

These findings, suggesting that most patients with aUC will receive only a single line of therapy, place particular emphasis on the importance of first-line therapies. Since many patients may not have the opportunity to receive further treatments, the decision regarding first-line therapy becomes particularly crucial. Further studies should be undertaken to better understand why so few patients are able to receive second-line therapy. The natural history of aUC indicates that many patients can experience rapid progression once treatment becomes ineffective. This may prevent these patients from accessing subsequent lines of therapy if additional treatments that can work quickly are not available, and it underscores the importance of such treatments and close patient monitoring.

For many years, options in the treatment-refractory setting for patients with aUC were limited. However, this treatment landscape has evolved significantly in recent years with the approval of multiple agents such as pembrolizumab, erdafitinib, and enfortumab vedotin as monotherapy in the treatment-refractory setting. It is important to investigate whether these recent advances have influenced the treatment attrition rates for patients with aUC and whether more patients are now able to receive additional therapies beyond the first line. Improving these attrition rates poses a substantial challenge for the community of clinicians who treat patients with aUC. Education and
outreach efforts to both patients with aUC and their oncologists regarding additional available treatment options are of particular importance to decrease therapy attrition.

On the other hand, in a disease setting where many patients may be restricted to only a single line of therapy, selecting the most effective first-line treatment becomes essential. Looking forward, as the combination of enfortumab vedotin and pembrolizumab emerges as the preferred first-line treatment option for many treatment-naive patients with aUC, optimizing the use of this regimen will be of paramount importance. Once again, providing comprehensive education regarding intricacies of this treatment and potential adverse effects, as well as diligent patient monitoring, will be critical. The demonstrated improved efficacy of this regimen will likely allow more patients to have prolonged treatment benefit and may increase the likelihood of patients receiving subsequent lines of therapy.

Although substantial advances have been made in the care of patients with aUC, significant challenges remain. Even with improved first-line regimens that prolong the duration of response for many patients, most are unfortunately still not cured of their disease. Intensifying front-line therapy further may be an important next step, such as by combining therapies that would otherwise be used sequentially. Additionally, we still lack important biomarkers to help identify specific patients for specific treatments. This biomarker-driven patient selection is particularly relevant given the noted importance of first-line treatment. The availability of other novel frontline treatment regimens such as cisplatin, gemcitabine, and nivolumab, based on recent results from CheckMate-901 clinical trial, further highlight the potential importance of biomarker-driven therapy selection for treatment-naive patients with aUC.

Despite the inherent limitations of this retrospective study and the potential constraints of the database used, the assessment of treatment patterns used for patients outside of a clinical trial setting remains one of this study’s most important aspects. It highlights the challenges that most patients with aUC in the US are likely to encounter in these circumstances. This study offers valuable insights for ongoing treatment of patients with aUC that are informed by the high rates of therapy attrition observed in this patient population.

REFERENCES


