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CORRESPONDENCE

Determining fitness for enfortumab vedotin and pembrolizumab in metastatic bladder cancer: the time to move beyond isolated comorbidity assessments

Enfortumab vedotin and pembrolizumab (EV/P) are recommended as first-line management of advanced urothelial carcinoma (aUC) based upon EV-302; but multiple platinum-based and immunotherapy-containing options exist as alternatives.[1] This has sparked a discussion about how to identify who would most benefit from EV/P. Some advocate for the development of strict selection criteria, analogous to Galsky's cisplatin 'unfit' criteria.[2,3] Others argue against strict criteria and, instead, contend that clinical judgment be utilized to guide risk—benefit discussions based upon the toxicities of both medications.[4] Although with clear differences, both approaches rely upon assessments of comorbidities and end-organ function to predict fitness for EV/P. While we agree that this should be the backbone of treatment selection, evaluating fitness based upon these factors alone is insufficient in clinical practice. To truly optimize first-line management, the discussion must evolve. Just as molecular profile-driven treatment selection is becoming standard, biopsychosocial-driven treatment selection should be the norm. In aUC, where there are several first-line options for an older population, it is paramount that comprehensive functional, psychosocial and cognitive assessments be key components of choosing a therapeutic approach.

In EV-302, EV/P improved overall survival with comparable toxicity relative to platinum—gemcitabine combination therapy.[1] Still, 97.0% of patients experienced EV/P-related toxicity including 55.9% with grade $\geq$3 toxicities. Unique grade $\geq$3 toxicities included peripheral neuropathy, hyperglycemia, pruritis and maculopapular rash. Based upon these side-effects as well as EV's known toxicity profile, the EV-Ineligible criTeriA (EVITA) have been suggested.[2] These proposed criteria are not based upon consensus and an optimal EV selection criterion remains undefined. Importantly though, authors did include the Eastern Cooperative Oncology Group (ECOG) performance status (PS), which highlights a limitation of EV-302. In EV-302, only 23.7% of patients were $\geq$75 years old and 2.9% had an ECOG PS of 2, which is significantly different than clinical practice.

As EV/P is used in older and frail patients, the toxicity profile will be better understood, affording the opportunity to optimize biopsychosocial-driven treatment selection. The biopsychosocial model emphasizes the importance of psychological and social aspects of a patient's health in addition to comorbidites.[5] As an extension, in caring for older patients, oncologic societies recommend carrying out geriatric assessments (GAs). GAs are multi-modal evaluations of several health-related areas, including biopsychosocial-specific domains.[6] However, GA use is limited in aUC. In our national survey of 112 US-based genitourinary medical oncologists, all respondents consider frailty when making chemotherapeutic recommendations in aUC, but 90.2% (n = 101) never or almost never carry out comprehensive GAs.[7] Despite this, many respondents found multiple biopsychosocial domains to be critical in predicting fitness for chemotherapy. In addition to comorbidities, respondents identified mobility (87.5%), social support and living situation (81.3%), cognitive function (73.2%) and nutritional status (71.4%) as key factors in predicting chemotherapy tolerance.[7]

Clearly, a divide exists—physicians identify biopsychosocial factors as important, but they are not evaluating them using validated assessments. In the rapidly evolving landscape of aUC, at the same time that work is being done to identify new therapeutic approaches, research should aim to understand how biopsychosocial factors impact outcomes and tolerance. At the Dana-Farber Cancer Institute/Harvard Cancer Center, we are addressing questions surrounding optimization of care in older/frail patients with aUC in an ongoing prospective observation trial (Clinicaltrials.gov, NCT06138561) where we are comparing adverse events and quality of life in cisplatin-ineligible, frail patients receiving different standard-of-care therapies including EV/P. Our hope is that through this and similar work, a more comprehensive understanding of EV/P fitness will emerge to guide clinicians in optimizing the complex and nuanced process of treatment selection in older adults.

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