Editorial Commentary

Prognosis in high-grade T1 bladder cancer: host immune response and tumour infiltrating lymphocytes

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Bladder cancer is a heterogeneous disease that poses a challenge to the treating clinician. In non-muscle-invasive bladder cancer (NMIBC), the EORTC risk tables have helped stratify patients into low, intermediate and high-risk groups, but are now over a decade old (1). Within the high-risk group lies high-grade T1 (HGT1) disease, a variable group of patients with tumors that can behave similarly to muscle-invasive bladder cancer. Rates of progression to muscle-invasive disease and metastases vary between 25% and 73%, and long-term follow-up suggests up to 25% of patients may die from bladder cancer (2). Management of these patients can vary from immunotherapy to radical cystectomy, and a current unmet research need lies in stratifying patients who would most benefit from radical treatment.

Rouanne and colleagues (3) performed an interesting, multi-institutional study on tumor-infiltrating lymphocytes (TILs) in the setting of HGT1 bladder cancer. There is growing evidence that the extent and composition of the host immune response, in which TILs play a role, appears to have an impact on prognosis in many solid cancers (4). TILs are a diverse group of lymphocytes located around tumors cells, having been identified in primary tumors, lymph nodes, and metastases, and the ratios of these cells have implications in carcinogenesis. Research into TILs is therefore increasing, given its affordability and accessibility as a biomarker, and this may have value in predicting response to treatments, particularly in the setting of new immune checkpoint inhibitors and other forms of immunotherapy.

In this retrospective study, the authors analyze histological samples from 147 patients with HGT1 disease, scoring stromal TIL density, i.e., percentage of stromal area infiltrated by mononuclear inflammatory cells over the total intratumoral area. A positive association was seen between high TIL density and both tumor invasion depth (pT1b *vs.* pT1a disease, P=0.01) and variant tumor histology (P=0.01). Unfortunately, on Kaplan-Meier analysis, no statistical difference was found between high and low-density TIL tumors, for recurrence-free, progression-free, cancer-specific, or overall survival.

The authors should be commended for assessing TILs in a homogeneous cohort of patients, with long (median 8.2 years) follow-up. All specimens were reviewed independently by two pathologists. The use of the standardized method proposed by the International Immuno-Oncology Biomarkers Working Group will allow for comparisons to future studies (5). However, based on this study alone, assessment of TILs in high-grade NMIBC does not appear to be useful. The authors do conclude that tumor aggressiveness is associated with an increased adaptive immune response, as demonstrated by the higher baseline TIL level in T1b disease.

It is intriguing that there does not appear to be a link between TIL density and survival, despite a higher percentage of intense lymphocytic infiltration in the T1b tumor subgroup. Some bias may arise from the variations in postoperative follow-up and management. Bacillus

Calmette-Guerin (BCG) therapy was used in 121 patients, up-front radical cystectomy in 5 patients, and transurethral resection (TUR) in 21 patients. The study does not clarify how this proportion of radical cystectomy patients were followed-up; this management modality would have impacted on monitoring and type of disease recurrences. It is noted that initial management did not include early repeat TUR in all patients. Initial management of HGT1 disease has progressed in recent years, with the value of repeat TUR proven and included in guidelines (6); upstaging is as high as 32% in some studies (7). Both residual tumor and upstaging may have impacted on both recurrence-free and progression-free survival.

Within this study, there are questions which merit further investigation. It is still uncertain if HGT1 patients are best treated with intravesical maintenance BCG or radical cystectomy, and is the subject of current randomized controlled trials (8). According to current guidelines, BCG non-responders should be offered radical cystectomy due to the risk of progression to muscle-invasive disease (6). In the current study, 71 out of 121 patients were BCG non-responders; this moderately-sized cohort may provide valuable information about the association between TILs and BCG-responsiveness, identifying patients who would not benefit maintenance BCG and who should be offered up-front radical cystectomy.

Risk stratification for HGT1 disease remains a challenge for clinicians. While Rouanne and colleagues have provided us with the most extensive study of TILs in HGT1 bladder cancer, it raises new questions, including its role in immunotherapy and risk assessment. The immune system may still play a critical role in NMIBC survival and progression, with exciting future research avenues.

Acknowledgments

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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