Commentary

A step towards refining prognostication in individual patients with bladder cancer

The authors describe their experience of immunohistochemical (IHC) profiling of 49 cases of transitional cell carcinoma (TCC) of urinary bladder with CD10 and CA19.9 and correlate the positivity and intensity of staining with the WHO 2004 classification grade and American Joint Cancer Committee/Union Internationale Contre le Cancer (AJCC/UICC) stage of the tumors.[1] They found that both the positivity and the intensity of staining with both markers correlated strongly with the WHO 2004 grades of TCC but not with the stage. The authors conclude that IHC staining for these two markers could be of value in assisting the differentiation between low and high grade TCC and consequently in determining the prognosis in such cases.[1]

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Transitional cell carcinoma (TCC) constitutes the most common malignant tumor of the urinary bladder and the upper urinary tract throughout the world.[2] It poses significant diagnostic, prognostic, and therapeutic challenges to all the health care professionals involved in the care of these patients. Around 75% to 85% of cases of TCC present with superficial disease, i.e., pTa or pT1, and the disease in these patients is characterized by repeated recurrences in majority of patients and progression to muscle invasive disease in a small but significant number of cases.[1] These patients are put on lifelong surveillance program involving repeat cystoscopies, urine cytology, and surveillance biopsies.

This entails considerable economical burden to the patient and to the society. An accurate prediction of which patients will develop progressive disease remains a formidable challenge. Historically, the prognostication in individual patients has been mainly based on the clinicopathological parameters, such as number of tumors, configuration, grade, and stage. However, many of the pathological parameters such as grade and stage suffer from significant intra- and interobserver variability and sampling errors.[3] WHO 1973 classification dominated the practice for over three decades, but several shortcomings and controversies emerged over time, necessitating its thorough revision in late 1990s. WHO 2004 classification was developed to further standardize the criteria for grading and staging of these tumors. However, both WHO classifications for grading suffer from substantial interobserver variability, with the 2004 WHO classification showing less interobserver variability.[3] This has led to a persistent search for more robust parameters such as flow cytometry, chromosomal analysis, genomics, proteomics, IHC or molecular genetic markers for accurately predicting the disease course in individual patients.[1]

There are very few studies on the use of CD10 marking of TCC in the literature.[4,5] Still fewer studies are available on the IHC profiling of CA19.9 of this tumor.[6] The results from the studies have produced conflicting data.[1,4-6] There are no studies in the literature on the combined use of both CD10 and CA19.9 markers in TCCs of urinary bladder. The authors have done a commendable job in sharing their experience with this combination of markers. However, there are a number of caveats in the study. The authors have used the histopathological parameters of grade and stage as the gold standard for determining the correlation with IHC markers, the determination of which is also subjective. The authors should have used the clinical course of the disease as the gold standard, but the follow-up is too short to allow this. There are also many problems in the performance and standardization of IHC markers. Moreover, the demographics of the patients, their follow-up information and the treatment offered are not provided, which limit the power of the study. The authors included only low and high grade TCCs, and not the entire range of papillary urothelial neoplasms. The later approach might have been more helpful in better defining the reactivity of these markers.

Several other biomarkers have also been investigated to accurately prognosticate the disease, including individual cell cycle-related proteins such as p53, pRb, p16, p21, and p27. Other useful markers are the oncogene products of fibroblast growth factor receptor 3 (FGFR3) and the ErbB family, proliferation markers including Ki-67, Aurora-A, and survivin and components of the immune system. It has been demonstrated that, in single-marker analyses, the proliferation markers Ki-67, survivin, and Aurora-A offer the best potential to predict disease progression since they were all able to demonstrate independent prognostic power in repeated studies. Thus, although substantial improvement has taken place in understanding the disease with the use of IHC markers, none of them can be recommended for routine use at present.[7]

More recent studies assaying alterations in molecular pathways are likely to contribute valuable information that can accurately predict outcome and chemotherapeutic response in individual patients with TCC. Medium- to high-throughput gene-expression profiling technologies are now allowing multiplexed evaluation of changes responsible for the progression of these tumors. These investigations use either global or pathway-based approaches to define molecular signatures that can predict prognosis independent of traditional clinicopathological indices. The prognostic panels produced using these strategies can also elucidate the biology of tumor progression and identify potential therapeutic targets for tailored treatment.[8]

It is too early to draw any firm conclusions from this study due to the small number of cases, its retrospective nature, lack of treatment and follow-up data, but the prospects are promising. The authors are to be commended for their impressive study from a developing country addressing a challenging issue in tumor prognostication of a fairly common tumor, and are encouraged to expand this study prospectively with further follow-up of this group of patients to add to our knowledge.

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