

EDITORIAL

Prospects for Optimized Clinical Management of Bladder Cancer by Application of Phenotypic Markers

Randall E. Millikan, Christopher J. Logothetis*

The search for molecular markers that will permit the optimized individual management of patients with urothelial cancer is beginning to pay dividends. The findings reported by Stein et al. (1) in this issue of the Journal demonstrate the prognostic value of p21 expression, confirming the importance of p53-related pathways. However, further refinements will be required before p21 expression as assessed by immunohistochemistry can be exploited clinically. As is true for all markers, the clinical utility of this marker will ultimately depend on how p21 status can contribute to resolving the dilemmas of clinical management.

In our view, the principal therapeutic dilemmas in the management of patients with bladder carcinoma are as follows: 1) predicting whether organ preservation is feasible in selected patients, i.e., predicting which patients will have disease progression following intravesical therapy; 2) assessing the probability of a cure with total extirpation of the bladder, i.e., predicting the presence of occult, disseminated disease; and 3) predicting the sensitivity of a particular patient's cancer to available chemotherapy. The first dilemma is complex, requiring both cancer-specific markers and markers reflecting malignant potential; studies in this vein are in progress (2). Most studies reported to date are related to the second dilemma; very few studies have addressed the third. As shown in Table 1, previous studies have established the impact of p53 mutations and altered Rb protein expression on the prognosis of urothelial cancer (3). Whether p53 status and Rb status also predict for sensitivity to chemotherapy remains to be established. The dilemma of whether or not to offer a patient adjuvant chemotherapy is complex, depending on both the risk of relapse and the probability of responding to chemotherapy; these factors may not be independent, and as yet the relationship between them has not been established. At present, one *cannot* make decisions about adjuvant chemotherapy based solely on the probability of relapse; the very features responsible for relapse may also affect the probability of responding to chemotherapy.

The article by Stein et al. (1) is the latest in a series of correlative studies reported by the group at the Kenneth Norris Jr. Comprehensive Cancer Center, Los Angeles, CA, from a cohort of patients undergoing cystectomy from 1983 through 1988. These investigators have previously contributed to the recognition that p53 status and Rb status are strongly prognostic; they now report on p21 status, a logical extension to further

explore pathways related to p53 function. As previously reported in other contexts (4,5), these workers hypothesized that further refinement of the prognostic implication of p53 mutation would be possible by defining expression of p21, especially in light of recent evidence that p21 expression can be p53 independent.

The makeup of the study cohort is rather evenly split between patients with disease confined to the bladder (n = 115) and those with either extramural extension or involvement of regional lymph nodes (n = 127). Although not stated, it is likely that many of the patients in the latter category received chemotherapy. These patients with locally advanced disease do not represent a clinical management dilemma, since they are already recognized to benefit from systemic therapy. The patients with organ-confined disease are thus of greatest interest. In these patients, p21 positivity (present in 89 of 115 cases) was associated with a 13% rate of tumor recurrence at 5 years and an overall survival of 81%. By contrast, p21-negative tumors (26 of 115 cases) showed a recurrence rate of 49% and an overall survival of only 50%. Furthermore, the relationship between p53 phenotype and p21 status was explored. Although not reported specifically by stage, the overall results convincingly show that p21 status does stratify the group with an abnormal p53 phenotype. In fact, the survival among patients with a p53-altered phenotype, but with preservation of p21 expression, was similar to that among patients with normal p53 staining. Conversely, patients with both a p53-altered phenotype and loss of p21 had an especially poor prognosis. Again, the influence of chemotherapy on these results is unknown, and it would be inappropriate to assume that it is irrelevant until the appropriate studies are completed.

How should the practicing clinician apply these results to the treatment of patients with bladder cancer? Knowledge of p53 status and of p21 expression may aid in counseling patients with organ-confined cancer. Unfortunately, we do not yet have any information about how this marker might apply to the progression of superficial disease, or about the implications of p21 status on sensitivity to chemotherapy. Thus, to fully exploit

*Affiliations of authors: R. E. Millikan, C. J. Logothetis, Department of Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX.

Correspondence to: Randall E. Millikan, Ph.D., M.D., Department of Medical Oncology, University of Texas M. D. Anderson Cancer Center, Box 13, 1515 Holcombe Blvd., Houston, TX 77030-4095.

© Oxford University Press

Table 1. Overview of predictors of outcome in bladder cancer

Clinical challenge	Predictive clinical features*	Predictive phenotypic features*	Ref. No.
Organ preservation	Presence of c.i.s. (++) , T-stage (++) , non-papillary histology (+), and grade (+)	p53 (+), Rb (+), and EGFr (++)	(4,6)
Curative surgery	T-stage (++) and vascular invasion (++)	p53 (++) , Rb (++) , and p21 (+)	(1,4)
Response to chemotherapy	Performance status (++) , non-TCC histology (++) , elevated serum β -hCG (+), and visceral involvement (+)	p53 [†]	(4)

*((+)) = strongly predictive; (+) = moderately predictive; c.i.s. = carcinoma *in situ*; β -hCG = β -human chorionic gonadotropin; T-stage = tumor stage; TCC = transitional cell carcinoma; Rb = retinoblastoma protein; and EGFr = epidermal growth factor receptor protein.

[†]Predictivity of chemotherapy outcome with p53 is not adequately confirmed.

these findings, additional studies targeting specific, uniformly treated populations will be required. By expanding the important observations of the investigators from the Kenneth Norris Jr. Comprehensive Cancer Center to specific populations, bladder cancer may soon join the rank of human cancers in which molecular characterization drives therapeutic intervention. Performing these studies should be a high priority for investigators with an interest in bladder cancer.

References

- (1) Stein JP, Ginsberg DA, Grossfeld GD, Chatterjee SJ, Esrig D, Dickinson MG, et al. Effect of p21^{WAF1/CIP1} expression on tumor progression in bladder cancer. *J Natl Cancer Inst* 1998;90:1072–9.
- (2) Chaturvedi V, Li L, Hodges S, Johnston D, Ro RY, Logothetis C, et al. Superimposed histologic and genetic mapping of chromosome 17 alterations in human urinary bladder neoplasia. *Oncogene* 1997;14:2059–70.
- (3) Cote RJ, Dunn MD, Chatterjee SJ, Stein JP, Shi SR, Tran QC, et al. Elevated and absent pRb expression is associated with bladder cancer progression and has cooperative effects with p53. *Cancer Res* 1998;58:1090–4.
- (4) Wakasugi E, Kobayashi T, Tamaki Y, Ito Y, Miyashiro I, Komoike Y, et al. p21(Waf1/Cip1) and p53 protein expression in breast cancer. *Am J Clin Pathol* 1997;107:684–91.
- (5) Werness BA, Jobe JS, DiCioccio RA, Piver MS. Expression of the p53 induced tumor suppressor p21waf1/cip1 in ovarian carcinomas: correlation with p53 and Ki-67 immunohistochemistry. *Int J Gynecol Pathol* 1997;16:149–55.
- (6) Neal DE, Sharples L, Smith K, Fennelly J, Hall RJ, Harris AL. The epidermal growth factor receptor and the prognosis of bladder cancer. *Cancer* 1990; 65:1619–25.