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Re: Phase III Study of Molecularly Targeted Adjuvant Therapy in Locally Advanced Urothelial Cancer of the Bladder Based on p53 Status

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Experts' summary

Retrospective evaluations had suggested that p53 dysregulation is prognostic and predictive of response to cytotoxic chemotherapy in bladder cancer. This phase 3 study assessed tumors from postcystectomy patients with pT1–2 N0 M0 bladder cancer for p53 overexpression. Mutant p53 is *stabilized* and detectable by immunohistochemistry, whereas wild-type p53 is quickly degraded. Patients with p53-positive tumors were consented for randomization to methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (MVAC) chemotherapy versus observation. The study enrolled 521 patients over 8 yr at 39 institutions. The overall 5-yr probability of recurrence was 20%, with no difference noted between the p53-positive and -negative groups ($p = 0.23$). Additionally, for those with p53 positivity, the overall survival at 5 yr was 85% and was not different between those randomized to MVAC versus observation ($p = 0.89$).

Experts' comments

Despite the demonstrated survival benefit of cisplatin-based neoadjuvant chemotherapy [1], as reaffirmed with the long-term results of the phase 3 neoadjuvant (BA06 30894) study [2], only a minority of treated patients receives this benefit. Ideally, patient selection for chemotherapy would take place in two steps, by identifying patients with poor prognosis and then by utilizing predictive markers to select the most effective therapy for these patients. The trial by Stadler et al highlights the challenges of biomarker-defined treatment randomization. The first challenge is the time required over 8 yr to identify and enroll 114 p53-positive patients. Second, the trial was based on retrospective data on the value of p53 as a prognostic and predictive factor using various techniques for p53 expression assessment. These data were far from unanimous or robust, especially in showing that p53 expression was predictive of MVAC response. Recently, new prognostic markers for bladder cancer have been validated in prospectively collected data sets, including a 20-gene model that predicts pathologic nodal involvement at cystectomy [3]. Discovery of predictive markers is also advancing, including the use of the coexpression extrapolation, or COXEN,

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approach [4], which rapidly develops predictive multigene biomarker models for virtually any agent by correlating gene expression of untreated human bladder cancer tissues with gene predictors of in vitro cellular drug response. This technology will provide models that can theoretically predict response to specific therapy as well as offer novel drug options. New markers will need to be based on robust and reproducible analytic platforms that will require widespread support of the genitourinary cancer community to be rapidly validated on prospectively collected data sets or in clinical trials if such data sets are not available.

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