

vinblastine, doxorubicin, and cisplatin (MVAC) based on p53 genetic alteration. This study analyzed 499 patients with T1-T2N0 bladder cancer who had undergone radical cystectomy and pelvic lymph node dissection for p53 expression by immunohistochemistry. Subjects with altered p53 expression were then randomly assigned to three cycles of MVAC versus observation. The primary objective of this trial was to compare recurrence in patients with p53-positive tumors randomly assigned to MVAC versus observation. The secondary objective of the trial was to compare recurrence in the p53-positive and negative arms. Accrual was halted on the basis of an interim futility analysis. Overall 5-yr probability of recurring was 0.20 (95% confidence interval [CI], 0.16–0.24) with no difference on the basis of p53 status. Only 67% of patients randomly assigned to MVAC received all three cycles. The authors observed no prognostic value in p53 as a biomarker and no benefit of treatment with MVAC in p53-positive patients.

#### Experts' comments:

Recurrence rates of  $\leq 50\%$  are still observed in patients undergoing radical cystectomy [1]. Although cisplatin-based combination neoadjuvant chemotherapy improves survival, administration of neoadjuvant chemotherapy for all patients undergoing radical cystectomy has not been widely adopted. This may be due to concerns over unnecessarily treating many patients and/or the belief that adjuvant chemotherapy may be as effective as neoadjuvant chemotherapy if administered selectively based on adverse pathologic characteristics [2]. This trial sought to use a strategy of selected adjuvant chemotherapy based on p53 status of the tumor at cystectomy. P53 is a cell-cycle regulatory gene that is mutated in many cancers, including bladder cancer [3]. This molecular marker was chosen because of compelling observations of the association of p53 with poor outcome in bladder cancer and because p53 inactivation was thought to predict tumor susceptibility to DNA-damaging chemotherapy. This study was halted after a scheduled interim data analysis determined that no significant benefit was observed for patients randomized to the p53-positive treatment arm with MVAC.

This important study highlights the challenges of using data based on observational studies to design prospective trials. Unlike statistical power and level of significance, which are generally chosen by convention, the underlying event rate and the expectant treatment effect must be established by other means, including observational studies. The p53 trial suffered from a low event rate and a 21% noncompliance rate, which ultimately compromised the ability to interpret the

prognostic and predictive value of p53 tumor expression. This trial estimated a 20% absolute reduction in the probability of recurrence at 3 yr with an underlying event rate of 50%. In fact, the overall probability of recurring at 5 yr was only 20%. Despite convincing evidence for the poor prognostic value of p53, these patients were *low-risk* patients by conventional pathologic assessment (pT1–pT2). Although a survival advantage of adjuvant chemotherapy has not been definitely proven, the current data would indicate that if a survival advantage were to be gained, we would expect to see this in high-risk populations, such as patients with advanced pathologic stage and node positivity [4].

The authors should be commended for this pivotal trial in bladder cancer. At the current rate, the next decade will result in an overabundance of molecular markers and novel therapies whose investigation will require novel paradigms to scientifically prioritize their development. Concurrently, a similar emphasis should be placed on incorporating novel approaches to clinical trial design and patient selection [5].

**Conflicts of interest:** Robert S. Svatek has received financial compensation for participation in a scientific study/trial with Adolor Corp. and Alere Corp.

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William M. Hilton<sup>a</sup>, Robert S. Svatek<sup>b,\*</sup>

<sup>a</sup>US Air Force, Lackland AFB, San Antonio, TX, USA

<sup>b</sup>University of Texas Health Sciences Center San Antonio, San Antonio, TX, USA

\*Corresponding author. UTHSCSA, Urologic Oncology, 7703 Floyd Curl Rd, San Antonio, TX 78229, USA.  
E-mail address: svatek@uthscsa.edu (R.S. Svatek)

DOI: 10.1016/j.eururo.2012.02.011

#### Re: International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastin Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial

International Collaboration of Trialists on behalf of Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group), the European

Organization for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, the Australian Bladder Cancer Study Group, the National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, and Club Urologico Espanol de Tratamiento Oncologico Group

*J Clin Oncol* 2011; 29:2171–7

**Expert's summary:**

In this article, the authors present the final results of a large, multicenter, randomized, phase 3 trial comparing three cycles of cisplatin, methotrexate, and vinblastine (CMV) prior to local treatment versus local treatment alone in patients with muscle-invasive bladder cancer (MIBC). With a median follow-up period of 8 yr, the study demonstrates a 6% improvement in overall survival, with a reduction in risk of death of 16% ( $p = 0.037$ ) in favor of the neoadjuvant chemotherapy arm. These results, reaching the highest level of scientific evidence (level 1a), are in agreement with previously published data on neoadjuvant chemotherapy [1,2]. This approach is already regarded by many colleagues in the field of uro-oncology as a new gold standard in the therapeutic management of patients with MIBC.

**Expert's comments:**

The scientific evidence given by one randomized study or more should always be evaluated taking clinical relevance into account before any novel therapeutic strategy can be considered a standard of practice. In this respect, the analysis of this article raises few important issues that deserve further scrutiny.

First, is neoadjuvant chemotherapy cost-effective when compared to local therapy alone? The present study proposes an absolute difference in overall survival of 10% at 2 yr as clinically relevant; however, the study only observed a 6% difference at 8 yr, with a survival advantage of 7 mo, translating into a number needed to treat (NNT) of 17 to achieve 1 survivor more with neoadjuvant chemotherapy. These results are more modest than those initially considered clinically relevant. Chemotherapy undoubtedly adds morbidity, with reported rates of severe toxicity (grades 3 and 4) and mortality of 26% and 1%, respectively. Furthermore, neoadjuvant chemotherapy results in a delay of local treatment for a minimum of 3 mo, with the long-term impact of such delays still unknown. These issues should be taken into account and should form the basis of a constructive debate about the questionable clinical relevance of routinely implementing a neoadjuvant policy in patients with MIBC.

Second, the study includes patients with three different approaches to local treatment: radical cystectomy alone, preoperative radiotherapy, and radiotherapy alone. Because these approaches have different morbidity and mortality rates, they should be evaluated separately, using cancer-specific mortality as a more realistic and clinically relevant end point. With these criteria, radical cystectomy achieves an absolute difference in overall survival of 10% in favor of the CMV neoadjuvant arm, with a 26% reduction in the risk of death ( $p = 0.002$ ). The real difference in terms of cancer-specific survival is reduced to 3%, or to 1.4% when the cohort of neoadjuvant radiotherapy is added. These differences are unlikely to be statistically significant (data not mentioned in the article) and translate to an NNT ranging from 33 to 71. They raise concerns about the real benefit and the clinical relevance of neoadjuvant chemotherapy prior to radical cystectomy.

Third, in the case of radiotherapy, the absolute difference in terms of overall survival is reported as 6.4% in favor of the neoadjuvant cohort, representing a 20% reduction in the risk

of death ( $p = 0.07$ ). However, subset analysis of this cohort demonstrates a 7.1% difference in terms of cancer-specific mortality, which is likely to be statistically significant (although not mentioned in the article) and represents an NNT of 14. These findings suggest a potential clinical benefit of neoadjuvant chemotherapy prior to radiotherapy and, perhaps, a new standard of practice for patients opting for radiotherapy as local definitive therapy.

Fourth, would neoadjuvant chemotherapy be beneficial for all patients? The published analysis of the different subgroups would suggest that CMV is equally effective in all subgroups of patients in terms of overall survival, but a detailed description of the subgroups is not provided for further analysis. In contrast, the Southwest Oncology Group trial [2] reported a real benefit only in those patients reaching pT0 at the time of cystectomy—with transurethral resection of bladder tumor or with a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC)—representing a net survival benefit for only 23% of patients receiving neoadjuvant chemotherapy. In other words, 77% of patients receiving neoadjuvant chemotherapy potentially would be exposed to delays, toxicity, and mortality from chemotherapy without any added clinical benefit. These figures raise further concerns about the routine use of adjuvant chemotherapy. Moreover, we do not know which patients are chemoresponders. Future biomolecular markers may improve our knowledge and help us to select those who respond to chemotherapy, optimizing indications, to achieve satisfactory clinical relevance.

Finally, we should not forget that although the combination of cisplatin plus gemcitabine has less toxicity than CMV or MVAC, its efficacy remains to be proven in the neoadjuvant setting [3].

In summary, although the survival benefit observed in patients with MIBC treated with neoadjuvant chemotherapy is good news and is welcomed by the uro-oncology community, the clinical relevance of this improvement still remains controversial for standard of care.

**Conflicts of interest:** The author has nothing to disclose.

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Eduardo Solsona  
Instituto Valenciano de Oncología, Valencia, Spain  
E-mail address: solsona@pulso.com