Editorial Commentary

Biomarker challenges in the pursuit of personalized neoadjuvant chemotherapy for muscle-invasive bladder cancer: conclusions from SWOG S1314

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SWOG S1314, also referred to as the "COXEN trial", was a prospective randomized controlled trial designed specifically to test the performance of a transcriptomic classifier (COXEN, CO-eXpression ExtrapolatioN) to predict outcome after neoadjuvant chemotherapy (NAC) in patients with muscle-invasive bladder cancer (MIBC). The results for the primary endpoint, pathologic complete response, were reported previously, and now the secondary endpoints, overall survival (OS) and event-free survival (EFS), have been reported after longer term follow-up (1,2).

The COXEN algorithm is a novel approach to predict patient response to a specific drug therapy based on tumor gene expression that is matched to the gene expression of 60 well-characterized cancer cell lines [the National Cancer Institute (NCI)-60] and correlated to the therapeutic response of these cell lines *in vitro* to the same drug(s) (1-3). The NCI compiled gene expression for each cell line in the NCI-60 and the response of each to 45,000 different compounds and made this data available for public access. Urothelial carcinoma is not represented amongst the nine cancer types included in the NCI-60. To make the COXEN model more applicable to bladder cancer, its design incorporated the gene expression of a number of patient tumors and their associated response to neoadjuvant therapy. The model provides a predictive score for each patient based on the tumor's gene expression and the specific drug combination planned for administration. The COXEN model was validated retrospectively in multiple cohorts of patients with MIBC receiving NAC before being tested prospectively in S1314 (4,5).

SWOG S1314 was a phase II trial that randomized 167 patients with MIBC to 4 cycles of neoadjuvant gemcitabine-cisplatin (GC) or dose-dense methotrexate-vinblastine-adriamycin-cisplatin (ddMVAC) (1). Each patient's tumor tissue was used to derive a COXEN score, but this was not used to determine treatment in the trial. Two NAC regimens were included to allow the testing of a COXEN model for each regimen, but the study was not powered to compare oncologic outcomes between the two regimens.

The previous report of the trial's primary endpoint showed that COXEN did not predict pathologic response

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to GC or ddMVAC (1). In an exploratory analysis, the COXEN model for GC did predict pathologic response when patients treated with both NAC regimens were pooled. In the updated analysis with longer-term follow-up, Flaig et al. have reported that COXEN also fails to predict OS or EFS after either NAC regimen (2). Similar to the original analysis, the COXEN model specific to GC correlated with OS (but not EFS) when pooling both NAC arms [hazard ratio (HR) of 0.45; 95% confidence interval (CI): 0.20–0.99, P=0.047]. In this analysis only 43 (26%) of 167 patients had a favorable GC score, and the 5-year OS improved only from 71% to 76%, suggesting that the biomarker is missing a significant proportion of patients who benefit from NAC, and the response stratification is relatively weak. Furthermore, the wide CIs suggest that this is not a particularly robust prediction. Since this was not the intended population for analysis, this result must be considered hypothesis-generating.

It is interesting to consider why the GC but not the ddMVAC model correlated with OS in the pooled cohort. Although the COXEN model has been validated in multiple clinical cohorts treated with multiagent chemotherapy, the prediction scores for combination regimens are derived from computational compilation of the scores for each agent alone. This may negatively impact the fidelity of the biomarker, especially when four agents (ddMVAC) as opposed to only two agents (GC) are used (1,3). Since cisplatin is the dominant agent in both regimens, it is perhaps not surprising that there is overlap in the predictive capacity of the GC model to patients treated with ddMVAC. The larger sample size of the pooled cohort likely also contributes to the statistical significance of the GC model in the pooled cohort.

The authors should be commended for the robustness of this study with its prospective, randomized design intended to provide definitive validation of a complex biomarker with respect to appropriate oncologic outcome measures. Strict exclusion of patients receiving less than three cycles of chemotherapy, those with inadequate tissue for diagnosis, and those with inadequate follow-up strengthened the results of the trial, as did the relatively long median follow-up of 53 months (interquartile range, 43–62 months). The negative results of this trial are disappointing, because a positive result would have represented a critical advance in the field. A positive result would have allowed us to select the best patients for each NAC regimen based on the biomarker, and it would have identified likely non-responders who could proceed with alternative definitive therapies. Unfortunately, it appears at this time that COXEN will not be tested further as a biomarker to select NAC in patients with MIBC.

Independent of the performance of the COXEN biomarker, other important results can be taken from this trial. The 5-year OS after NAC and radical cystectomy was 90% for patients with ypT0N0 stage at the time of surgery (n=65), 89% for those down-staged to non-muscle invasive bladder cancer (pTis/Ta/T1N0; n=34), and 52% for non-responders with residual MIBC or nodal involvement (n=93). The HR for OS in those with a complete response or down-staging compared to non-responders was 0.14 (95% CI: 0.06–0.29; P<0.0001). These numbers are similar to previously reported results (6-10). Importantly, the results in this prospective trial support the use of pathologic response as a surrogate endpoint in clinical trial design which previously has been strongly associated with OS (11).

Although it must be emphasized that this trial was not powered to assess a difference in OS or EFS between the treatment arms, it is nonetheless noteworthy that there was no statistical difference in OS or EFS between the two NAC regimens. In the intention to treat population (n=227), the HR comparing ddMVAC to GC was 0.86 (95% CI: 0.59–1.26; P=0.44) for EFS and 0.87 (95% CI: 0.54–1.40; P=0.57) for OS. The last date of contact was used as the censoring date instead of last date of disease assessment, which could lead to some inaccuracy in the assessment of EFS. The results of S1314 need to be viewed in comparison to those of the prospective randomized VESPER trial in 437 patients with MIBC which demonstrated better 3-year progression-free survival (PFS) in patients treated with 6 cycles of neoadjuvant ddMVAC (66%) compared to 4 cycles of neoadjuvant GC (56%, HR =0.70; 95% CI: 0.51–0.96, P=0.025) (10). Other than the much larger sample size, the use of 4 versus 6 cycles of ddMVAC may explain some of the differences between the trials.

Although the COXEN algorithm did not predict outcome of NAC, biospecimens from the same trial have been used to test the impact of other candidate predictive biomarkers in this context. One important example is an exploratory study of plasma cell free DNA (cfDNA) methylation using the Infinium MethylationEPIC BeadChip array (Illumina, San Diego, CA, USA) on blood samples collected from 72 patients before and after one cycle of NAC with either GC or ddMVAC (12). In this study, the authors generated a classifier predictive of treatment response based on differential methylation between responders (≤ ypT1N0) and non-responders.

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Their "methylation-based response score" (mR-score) was predictive in samples taken before NAC and in those taken after the first cycle of NAC. They also used novel methods built on tissue-specific methylation patterns to estimate the fraction of cfDNA that originated from the bladder and identified a correlation between this parameter and response to NAC. By combining circulating bladder DNA fraction and mR-score, the authors were able to predict pathologic response (≤ pT1N0) correctly in 45 (79%) of 57 patients (12). The results of this exploratory analysis will require validation in larger cohorts. It remains to be seen if the authors will also report on the utility of circulating tumor (ct)DNA to predict response to NAC. Recent publications suggested that detection of ctDNA before NAC and persistence of ctDNA after NAC are predictors of poor outcome (13,14).

The same transcriptomic microarray data that were used to assign COXEN scores was also used to assign RNA-based molecular subtypes (15). The authors tested three different classifiers [The Cancer Genome Atlas (TCGA), the MD Anderson, and the Consensus classifiers] and condensed the TCGA and Consensus models into three subtypes. The condensed TCGA classifier consisted of basal-squamous/neuronal, luminal, and luminal infiltrated, and the condensed consensus classifier included basal-squamous/neuroendocrine, luminal, and stroma-rich (15). The results were somewhat discrepant between the models, and none of the models were able to predict complete response (ypT0) or downstaging (ypT2) after NAC (15). The subtype classifiers did not correlate with PFS or OS. Similarly, subtyping of 296 patients from the VESPER trial according to the Consensus classifier did not correlate with pathological response (16). A critical limitation of both analyses is the lack of comparison to a cohort of patients who were not treated with NAC. This leaves us unable to determine whether NAC is associated with a survival benefit compared to patients treated without NAC specifically in one or more subtypes. Prospective trials will determine the clinical utility of molecular subtyping in the neoadjuvant setting.

Genomic alterations in DNA damage repair genes have also been linked to response to NAC in multiple studies. In particular, pathologic complete response is enriched in patients with mutations in *ERCC2*, *FANCC*, *RB1* and *ATM* (17-21). Patients with an alteration in one or more of these genes also have excellent OS in the short term after treatment. One could anticipate that these gene alterations will also be tested in the S1314 cohort.

In conclusion, SWOG S1314 was a remarkable trial because it was designed specifically to test a biomarker for prediction of outcome to NAC. Unfortunately, the COXEN model could not be validated, and the trial has therefore not had an immediate impact on clinical practice. Nonetheless, the biospecimens collected on the trial have enabled investigation of multiple other biomarkers in this context. Developing a biomarker to select optimal bladder cancer patients for NAC remains a critical unanswered question.

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