Clinical outcomes associated with expression of aurora kinase and p53 family members in muscle-invasive bladder cancer

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Abstract. Biomarkers are needed in muscle-invasive bladder cancer (MIBC). We previously reported that high tumor aurora kinase (AURK) A expression identifies patients with MIBC with poor prognosis. Aberrant p53 expression has also been associated with poor outcomes in MIBC, though to the best of our knowledge, co-expression rates of p53 and aurora kinases have not been previously described in MIBC. As aurora kinase and p53 family members may co-regulate each other, the present study investigated whether tumor p53 or p63 protein expression influenced the prognostic value of AURKA in a pilot study of 50 patients with MIBC treated with curative intent. Immunohistochemistry for AURKA, AURKB, p53 and p63 were performed on archival pre-treatment tumor specimens and correlated with clinical outcomes in patients with MIBC who received neoadjuvant chemotherapy (NAC) prior to cystectomy. Baseline p53 [hazard ratio (HR) 1.46; 95% confidence interval (CI)=0.55-3.9; P=0.448) and p63 (HR 2.02; 95% CI=0.51-8.1; P=0.313) protein expression did not predict for overall survival (OS). Low p53 protein expression did not correlate with high AURKA (φ=0.190) or AURKB (φ=0.075) expression. However, in tumors with low p53 expression (n=17), the presence of either high AURKA or AURKB expression levels predicted an increased risk for relapse (HR 27.1; 95% CI=2.7-270.1; P=0.005) and mortality (HR 14.9; 95% CI=2.3-95.6; P=0.004) compared to tumors with both low AURKA and AURKB levels. The relationship between p63 and AURKA/B expression levels was not tested due to the prevalence (80%) of high p63 expression in the present cohort. In tumors with low AURKA expression, p53 status did not predict for OS (HR 0.62; 95% CI 0.2-3.2; P=0.572). In multivariable analysis, only high baseline AURKA expression predicted for inferior OS (HR 4.9; 95% CI 1.7-14.1; P=0.003). To the best of our knowledge, the present study was the first to report co-expression of p53 and aurora kinase family members in MIBC, and although wild-type p53 may regulate the aurora kinases in preclinical models, the adverse prognostic value of tumor AURKA overexpression was independent from baseline tumor p53 protein expression in the present cohort. AURKA remains an important prognostic biomarker in patients with MIBC and warrants further evaluation in prospective studies to validate whether baseline AURKA can identify patients that are unlikely to benefit from standard of care with NAC.

Introduction

Aurora kinases A and B (AURKA) and (AURKB) are essential for mitosis, though overexpression produces centrosome amplification, aneuploidy and resistance to apoptosis (1-3). Across multiple cancer types, including localized bladder cancer (4-11), overexpression is associated with poor prognosis and may contribute to cisplatin resistance (1,12). We recently investigated the prognostic value of AURKA and AURKB protein expression in a cohort of muscle-invasive bladder cancer (MIBC) patients treated with neoadjuvant platinum-based chemotherapy (NAC), based on the premise that aurora kinase over-expression may contribute to chemoresistance and poor outcome. In this cohort, we found that high baseline AURKA levels were prognostic for inferior relapse-free (HR=3.88, P=0.008) and overall (HR=6.10, P<0.001) survival in this study. Similar trends were observed with AURKB expression (13).

A co-regulatory interplay between the tumor suppressor p53 and the aurora kinases has been previously described raising the question of whether co-expression patterns may have prognostic value in cancer (14). Mutations in the TP53 gene are the most commonly detected somatic mutation in urothelial bladder cancer (15). Before the widespread use of next-generation sequencing, detection of p53 nuclear protein accumulation by immunohistochemistry (IHC) was used as a reliable proxy for mutant TP53 gene status (16,17). Multiple retrospective studies have suggested that p53 protein over-expression may confer an adverse prognosis In localized

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bladder cancer (18-20). However, results from a prospective, randomized trial failed to validate both the adverse prognostic value of baseline p53 over-expression and the potential predictive value in the context of adjuvant chemotherapy use (21), so further efforts to utilize p53 as a biomarker in bladder cancer have been largely abandoned.

Due to the potential co-regulation, the prognostic value of p53 may be influenced by aurora kinase co-expression status in bladder cancer and has not yet been reported. Both AURKA and AURKB phosphorylate p53, which impairs transcriptional activity leading to chemoresistance (1,12,22). p53 can reciprocally inhibit AURKA directly through transcriptional repression or indirectly through expression of p53 target genes that inhibit AURKA activity (23,24). The regulatory loop is supported by the observation that mutant p53 is associated with overexpression of AURKA in other tumor settings (25). p53 target genes are also implicated in regulation of AURKB stability, suggesting that p53 may be an important global regulator of the aurora kinase family of proteins (26).

Additional homologues of the p53 gene have also been discovered and share conserved DNA-binding domains which may regulate expression of overlapping target genes (27). Little is known about the potential contribution that p53 family members (p63 and p73) may also play in regulation of the aurora kinases, but preliminary data suggest that shared properties may exist (28). Expression of deltaNp63 (dNp63), a dominant-negative p53 homologue that can repress transcription of p53 pro-apoptotic target genes, commonly occurs in urothelial carcinoma but not in benign urothelium (29-31). Given the potential for co-regulation between p53 and aurora kinase family members, we hypothesized that tumor p53 status may impact the prognostic value of baseline AURKA expression. Since an unmet need exists for biomarkers to identify which MIBC patients are most likely to respond to NAC, we conducted a pilot study to determine whether p53 and p63 expression status may improve the prognostic value of baseline tumor AURKA expression.

Materials and methods

Patients. Following institutional review board protocol approval, a cohort of fifty consecutive patients with muscle-invasive urothelial carcinoma of the bladder who received neoadjuvant platinum-based chemotherapy followed by radical cystectomy diagnosed between July 2009 and August 2016 were retrospectively identified from an institutional tumor bank as previously described (13). Eligible patients included those with available archival pretreatment specimens for study analysis who received neoadjuvant platinum-based chemotherapy prior to radical cystectomy. Hematoxylin and eosin stained slides from study cases were reviewed by two tumor pathologists (CL, AH) to confirm adequate tumor cellularity for analysis. Formal statistical methods to estimate sample size were not utilized, because the co-expression rates of aurora kinase and p53 family members has not been previously reported and thus assumptions regarding expression rates and potential clinical outcomes were considered exploratory.

Immunohistochemistry. Formalin-fixed paraffin-embedded tumor blocks from diagnostic transurethral resection specimens were sectioned at 4 microns on positively charged glass slides and stained with the following immunohistochemical antibodies: aurora kinase A (polyclonal ab12875, 1:250 dilution, Abcam), aurora kinase B (polyclonal ab2254, 1:250 dilution, Abcam), p53 (D07, predilute, Leica Biosystems), and p63 (4A4, 1:50, Biocare Medical). Control tissue for all staining runs consisted of tissue microarray cores of human tonsil and urothelial carcinoma (positive controls) and normal thyroid (negative control). For both aurora kinase antibodies, expression was scored based on the percentage of tumor cells showing positive staining. For both p53 and p63, expression was scored based on the percentage of tumor cells showing positive nuclear staining. Tumor overexpression of AURKA and AURKB were defined as the upper quartiles for this cohort. Overexpression of p53 and p63 was defined as greater than 10 and 50% of tumor cells showing positive nuclear staining, respectively. A prognostic protein overexpression threshold previously defined was utilized for p53 staining (20). All slides were scored manually by an experienced surgical pathologist.

Statistics. Survival was calculated from the day of MIBC diagnosis. Chi-square and phi coefficient tests were used to assess the relationship between p53/p63 expression and AURKA and AURKB. Logistic regression models were used to determine the impact of pre-NAC expression on pathologic staging at cystectomy. Kaplan-Meier and Cox proportional hazards models were used to assess relationship with relapse-free and overall survival. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Co-expression of p53 and aurora kinase family proteins in MIBC. We have previously reported detailed clinical patient characteristics and aurora kinase expression patterns for this patient cohort (13). Representative examples of p53, p63, AURKA and AURKB protein expression from treatment naïve tumor specimens are shown in Fig. 1. High p53 protein expression has been demonstrated to correlate with the presence of an underlying TP53 gene mutation and separately to confer an adverse prognosis regardless of mutation status (16-18). High (>10%) p53 protein expression was observed in 33 (66%) tumors; whereas high (>50%) p63 protein expression was observed in 40 (80%) tumors.

The relationship of protein co-expression in pretreatment TURBT specimens was analyzed. Co-expression rates of p53 and aurora kinase family members is shown in Table I. Most tumors (15/17) with low p53 protein expression demonstrated high p63 expression, (phi=-0.148) due to the prevalence of p63 overexpression. However, low p53 protein expression levels were not associated with AURKA (phi=0.190) or AURKB expression (phi=0.075).

Baseline tumor p53 and aurora kinase family expression and pathologic response rate. We previously reported that baseline AURKA and AURKB expression did not predict for pathologic response to NAC; however, both high baseline AURKA

Table I. Co-expression of p53 and aurora kinase family members.

	p53		p63	
Aurora kinase	High (n=33)	Low (n=17)	High (n=40)	Low (n=10)
Aurora kinase A				
High	6	6	11	1
Low	27	11	29	9
Aurora kinase B				
High	8	3	8	3
Low	25	14	32	7

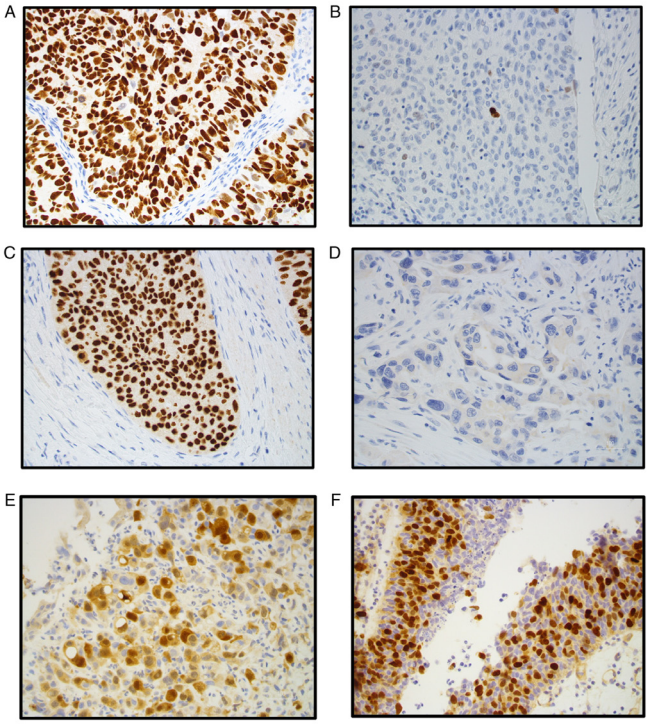

Figure 1. Representative protein expression by immunohistochemistry in untreated primary tumor samples. Protein and profiles were as follows: (A) p53, high; (B) p53, low; (C) p63, high; (D) p63, low; (E) aurora kinase A, high; (F) aurora kinase B, high. Brown chromogen staining in cells is interpreted as positive, blue hematoxylin counterstain highlights background histology (magnification, x200).

expression and ypT2 or greater tumor stage predicted for inferior overall survival (OS) in this cohort (13). In the current study, we also assessed whether baseline tumor p53 and p63 protein status may predict for pathologic response. Univariate analysis of baseline low p53 expression did not predict for pathologic complete response (pCR) [OR 0.82 (0.211-3.19), P=0.775]; however, baseline low p63 expression was associated with increased likelihood of pCR [OR 7.1, (1.6-31.8), P=0.011]. Only two of ten patients with low p63 expression also had low p53 expression.

Since the aurora kinases may impair p53 function, we next examined whether high AURKA or AURKB is associated with the response to NAC in tumors with low p53 protein expression. High AURKA or AURKB expression was observed in 6/17 (35%) tumors with low p53 expression and was not associated with pCR (OR 1.0, 95% CI 0.2-5.1, P=1.0). The potential relationship between p63 and AURKA/AURKB expression could not be evaluated due to our cohort size and the high observed rate of p63 overexpression. Only 3/10 tumors with low p63 expression demonstrated high AURKA or AURKB expression in this cohort.

Baseline tumor p53 and p63 expression and survival. Prior studies have reported conflicting results regarding the prognostic value of baseline p53 protein expression in localized bladder cancer; however, these studies did not examine the potential confounding impact of deltaNp63 co-expression. We therefore investigated the prognostic impact of p53 and p63 protein expression on relapse free survival (RFS) and OS using Cox proportional hazards models.

Baseline p53 expression level did not predict for RFS (HR=1.0 95% CI 0.34-2.94, P=0.995) or OS (1.46 95% CI=0.55-3.9, P=0.448) in this cohort (Fig. 2). Low baseline p63 expression did correlate with inferior RFS (HR 4.32, 95% CI 1.3-14.4, P=0.042), though an inferior correlation with OS was not statistically significant (HR 2.02 95% CI 0.51-8.1, P=0.312). The association between p63 expression and survival should be interpreted with caution based on the small cohort size, since one of the ten patients with low p63 expression was lost to follow up within two months after cystectomy.

Relationship of aurora kinase and p53 expression on survival. Although we did not observe a relationship between p53 protein levels and AURKA or AURKB expression, we examined whether aurora kinase expression may correlate with survival stratified by p53 status. As anticipated, in the subset of tumors with low p53 expression (n=17), the presence of either high AURKA or AURKB expression predicted for an increased risk for relapse (HR 27.1 95% CI=2.7-270.1, P=0.005) and death (HR 14.9 95% CI=2.3-95.6, P=0.004) compared to tumors with both low AURKA and AURKB. However, in the subset of tumors with low AURKA expression (n=38), p53 status did not clearly predict for RFS (HR 0.472 95% CI 0.09-2.5, P=0.373) or OS (HR 0.62, 95% CI 0.2-3.2, P=0.572). To investigate the relationship further, we performed multivariable analysis, and after controlling for high p53, high AURKA and AURKB and pathologic complete response, only baseline high AURKA was an independent predictor for inferior OS (HR 4.9, 95% CI 1.7-14.1, P=0.003).

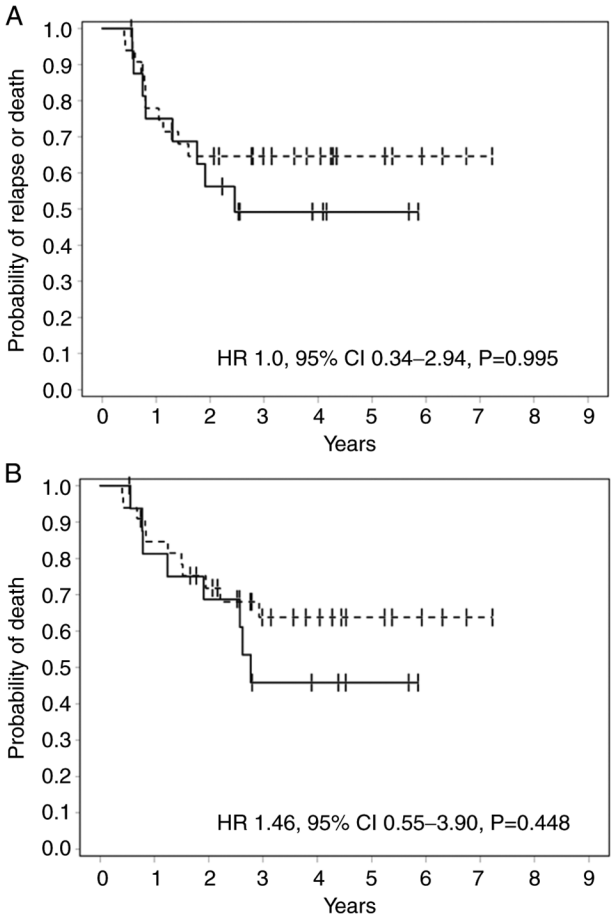

Figure 2. Survival by baseline p53 expression level. (A) Relapse free and (B) overall survival by p53 protein status (high expression levels indicated using - - -; low expression levels indicated using ——). HR, hazard ratio; CI, confidence intervals.

Discussion

We present results from the first known analysis of aurora kinase and p53 family member protein co-expression from a substantial cohort of patients with MIBC that received standardized neoadjuvant platinum-based chemotherapy. Independently, aberrant function of p53 and the aurora kinases have been associated with resistance to platinum-based chemotherapy (32,33). Since a co-regulatory feedback loop between wild type p53 and aurora kinase family members has been established in preclinical models, we tested whether the expression status of p53 and homologue p63 could influence the established prognostic value of AURKA or AURKB. Multivariable analysis confirmed the previously described adverse prognostic value for baseline high AURKA tumor expression, independent from p53 protein status [OS (HR 4.9, 95% CI 1.7-14.1, P=0.003)]. In the more favorable prognosis tumors with low aurora kinase expression, no relationship with p53 status was observed [OS (HR 0.62, 95% CI 0.2-3.2, P=0.572)] in this cohort. Our findings support prior observations that univariate analysis of baseline p53 protein expression does not predict for poor survival in patients with MIBC treated with peri-operative platinum-based chemotherapy. Furthermore, the prognostic value of baseline AURKA expression does not appear to be impacted by p53 status. Regarding the potential impact of p63 overexpression, formal analysis of the relationship between p63 and aurora kinase expression could not be performed due to the censor rate and small patient number with low p63 expression in this cohort.

While the total number of cases mandates a need for cautious interpretation of our findings showing lack of prognostic correlation, the strong positive correlation with baseline AURKA expression that we report reflects significant underlying biology. A potential limitation of our study is lack of concurrent analysis of the alternate p53 homologue, p73 (27). Little is known about p73 protein expression in bladder cancer since widely validated diagnostic antibodies are not available. However, preliminary studies of RNA expression suggest a pattern similar to p63, characterized by loss of the tumor suppressive TAp73 isotypes with increased local tumor stage and poor outcome (34,35).

We also did not assess *TP53* gene mutation status in these specimens. Since concordance between p53 protein expression and gene mutation status has been previously reported, we presumed that low protein expression correlated with wild type gene status in our study. However, we also chose to analyze p53 protein expression by IHC to mirror the techniques utilized by earlier studies that implicated a prognostic role for p53 expression analysis in local bladder cancer.

Since we did not observe an obvious correlation between p53 and aurora kinase expression levels in this study, it is worth noting that the co-regulatory interplay between the aurora kinases is best characterized with wild type p53 and may be altered in the setting of *TP53* gene mutations (14). The potential interaction between the aurora kinases and mutant p53 proteins may vary depending on the specific *TP53* mutation site and resulting impact on the expressed mutant protein and was not investigated in this study. The retrospective nature of this study and cohort size may have confounded results, though consecutive, eligible patients were selected in effort to mitigate potential selection bias. We did not perform molecular subtyping to exclude unintentional enrichment of a particular subtype that may have influenced patient outcomes (36).

Although we did not detect a prognostic relationship of p53 and aurora kinase family co-expression in this cohort of patients who received platinum-based chemotherapy, it remains unknown whether p53 status may have prognostic value in the setting of therapeutic aurora kinase inhibition. As monotherapy, the selective AURKA inhibitor alisertib showed limited efficacy in advanced urothelial carcinoma (37). However, preclinical studies suggest tumor cell apoptosis in response to AURKA inhibition may be dependent upon intact p53 or p73 function (38,39). Continued study of p53 as a potential predictive biomarker should be considered to accompany future development of aurora kinase inhibitors.

Neoadjuvant cisplatin-based chemotherapy prior to cystectomy remains standard of care in eligible MIBC patients (40). No predictive biomarker to identify which patients are most likely to benefit from NAC has been validated for routine clinical use. We previously showed that AURKA overexpression correlates with a poor prognosis in this setting (13), but whether high AURKA expression is also a predictive marker that identifies patients unlikely to benefit from NAC

is unknown. The aurora kinases contribute to chemoresistance though regulation of p53 family members in preclinical models. Although we did not find a prognostic relationship of co-expression of p53/aurora kinase family members in the present study, the adverse prognostic value of AURKA was again demonstrated independent from p53 status. These results underscore the potential importance of AURKA as a possible biomarker in MIBC patients receiving NAC and support future study to determine if high baseline AURKA may predict which patients are likely not to benefit from NAC and thus may be spared from potential treatment related toxicities in the absence of anticipated therapeutic benefit.

In summary, our results are consistent with prior studies that failed to identify prognostic value associated with p53 protein expression in patients with MIBC who received peri-operative chemotherapy (21). Although co-regulatory feedback loops may exist between the aurora kinase and p53 family members, p53 protein status did not impact AURKA prognosis in our analysis. These results are contrary to the relationship hypothesized by preclinical models and suggests that wild type *TP53* gene status does not mitigate the adverse prognostic value of AURKA expression in MIBC patients (23). However, our results do not rule out the possibility that expression of the p53 family members may be relevant biomarkers in the context of therapeutic aurora kinase inhibition, which may be of greater interest as aurora kinase inhibitors are tested in the clinical setting. Importantly, these results support the continued investigation of the potential predictive value of baseline tumor AURKA expression in patients with MIBC.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

EFB, CL, ST and DR conceived and designed the present study. HFO provided administrative support. EFB, CL and AH provided study materials. EFB, CL, ST, HFO and AH collected data and created the figures and tables. EFB, ST, JZ, PEC, CG and DR analyzed and interpreted the data. EFB and ST confirm the authenticity of all the raw data. All authors wrote the manuscript. All authors have read and approved the final manuscript. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Genitourinary Scientific Review Committee of the Levine Cancer Institute of Atrium Health and Advarra IRB (approval No. Pro00013882), and individual consent for this retrospective analysis was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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