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Laboratory-Bladder cancer

High aurora kinase expression identifies patients with muscle-invasive bladder cancer who have poor survival after neoadjuvant chemotherapy

Earle F. Burgess, M.D.*, Chad Livasy, M.D., Sally Trufan, M.S., Aaron Hartman, M.D., Renato Guerreri, B.S., Caroline Naso, B.S., Peter E. Clark, M.D., Claud Grigg, M.D., James Symanowski, Ph.D., Derek Raghavan, M.D., Ph.D.

Levine Cancer Institute, Atrium Health, Charlotte, NC

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Abstract

Objectives: Overexpression of aurora kinase A (AURKA) confers a poor prognosis in patients with urothelial carcinoma of the bladder. The prognostic value of high aurora kinase B (AURKB) expression in local bladder cancer is not well defined, and whether the prognostic value of either AURKA or AURKB is affected by the use of chemotherapy is unknown. We sought to characterize the impact of high AURKA and AURKB expression on clinical outcome in patients with muscle-invasive bladder cancer (MIBC) who received neoadjuvant chemotherapy (NAC).

Materials and methods: Immunohistochemistry for AURKA and AURKB was performed on pretreatment diagnostic transurethral resection of bladder tumor (TURBT) and matched cystectomy specimens in 50 subjects with MIBC who received NAC. Receiver operator characteristic curves (ROC) were calculated to assess the impact of AURKA and AURKB expression on pathologic response rate. Kaplan-Meier techniques and Cox proportional hazards models were used to assess the association with relapse-free survival (RFS) and overall survival (OS).

Results: Twenty-two of 50 [44%] patients had residual muscle-invasive (ypT2-4) urothelial carcinoma after NAC. Neither baseline tumor expression of AURKA (ROC = 0.57, $P = 0.46$) nor AURKB (ROC = 0.56, $P = 0.87$) predicted for ypT2-4 status. However, baseline expression of AURKA above the 75th percentile for this cohort was associated with an inferior RFS, (HR = 3.88, $P = 0.008$) and OS, (HR = 6.10, $P < 0.001$). Similar trends for worse survival outcomes were also observed for high AURKB levels (RFS, [HR = 2.2, $P = 0.13$] and OS, (HR = 2.25, $P = 0.09$).

Conclusions: High baseline tumor AURKA and AURKB expression identified MIBC patients with inferior RFS and OS despite the use of NAC and may identify patients who should be prioritized for clinical trial enrollment rather than standard cisplatin-based chemotherapy.

Keywords: Aurora kinase; Bladder cancer; Urothelial carcinoma; Chemotherapy

1. Introduction

Neoadjuvant cisplatin-based chemotherapy increases median survival by up to 3 years and the likelihood of cure by approximately 5% in patients who undergo radical cystectomy for muscle-invasive bladder cancer (MIBC) [1]. Subset analysis has shown that patients who achieve a pathologic complete response (pCR) following neoadjuvant chemotherapy (NAC) have improved survival compared to patients with residual disease, indicating that pathologic response may be a surrogate marker for chemosensitivity [2]. Despite a proven survival benefit, the use of NAC remains low due to concerns over treatment related toxicity and patient ineligibility [3]. For this reason, great need remains to identify predictive markers to determine which patients are most likely to benefit from NAC to encourage utilization in this population.

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*Corresponding author. Tel: 980-442-0410; fax: 980-442-9402.

E-mail address: earle.burgess@atriumhealth.org (E.F. Burgess).

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The 3 members of the aurora kinase family of serine/threonine kinases (aurora kinases A, B, and C) regulate cell division and maintenance of genomic stability. Overexpression of AURKA and AURKB can be transforming, induce chromosomal instability in vitro and is frequently observed in many human tumors [4]. Overexpression of AURKA can also promote tumorigenesis through inhibition of p53 proapoptotic functions [5]. In renal cell carcinoma, a regulator of AURKA, TPX2, predicts for adverse pathologic features and tumor recurrence [6].

Overexpression of AURKA has been reported in urothelial carcinoma of the bladder [7–12]. Expression of AURKA is uncommon in normal urothelium though increases with tumor stage in urothelial carcinoma [7]. Correlation of AURKA overexpression with inferior disease-free and overall survival was observed in 2 retrospective studies of patients with both nonmuscle-invasive and muscle-invasive bladder cancer [8,10]. In these studies, patient treatment histories were not reported, so the impact of specific treatment modalities on the prognostic value of AURKA expression in local bladder cancer remains unknown. Preclinical models also suggest that AURKA may be a viable therapeutic target in urothelial carcinoma, though a single agent study of the selective AURKA inhibitor alisertib in patients with advanced disease demonstrated limited activity [12,13].

AURKB overexpression has also been reported in urothelial carcinoma, although the prognostic value has not been extensively studied [12]. AURKA and AURKB have different subcellular localization, regulatory binding proteins and expression patterns during mitosis, which implies that overexpression of these proteins may carry independent prognostic value [4].

Tumor cell overexpression of AURKA or AURKB also contributes to cytotoxic chemotherapy resistance [14–18]. Both aurora kinases can regulate p53 activity and stability leading to impaired apoptosis [5,19,20]. Conversely, inhibition of both aurora kinases will enhance cisplatin sensitivity, which suggests that future therapeutic development of aurora kinase inhibitors may be optimally leveraged by combining with cytotoxic agents such as cisplatin [21,22].

Although overexpression of AURKA predicts for poor survival in patients with local bladder cancer, the impact of AURKB expression is poorly characterized. Furthermore, preclinical observations suggest that AURKA or AURKB overexpression in patients with MIBC may predict for resistance to neoadjuvant cisplatin-based chemotherapy; however, this has not been previously reported. Biomarkers to identify patients with MIBC unlikely to benefit from NAC are needed, so we conducted a pilot study to determine whether high baseline AURKA or AURKB tumor expression predicted for inferior survival in patients with MIBC after neoadjuvant platinum-based chemotherapy.

2. Material and methods

2.1. Patients

Following institutional review board protocol approval, 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 identified from an institutional tumor bank. Primary tumors containing an additional tumor histology were excluded from analysis. Patients were selected for study participation if paired archival tumor specimens from both pretreatment transurethral resection of bladder tumor (TURBT) and radical cystectomy were available for immunohistochemical analysis. Hematoxylin and eosin stained slides from study cases were reviewed by 2 tumor pathologists (C.L., A.H.) to confirm adequate tumor cellularity for analysis.

2.2. Immunohistochemistry

Formalin-fixed paraffin-embedded tumor blocks from cystectomy and 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) and aurora kinase B (polyclonal ab2254, 1:250 dilution, Abcam). 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 antibodies, expression was scored based on the percentage of tumor cells showing positive staining and average intensity of staining (0, 1+, 2+, or 3+). All slides were scored manually by an experienced tumor pathologist.

2.3. Statistics

Survival was calculated from the day of MIBC diagnosis. Univariable logistic regression models were used to determine the impact of pre-NAC expression on pathologic staging at cystectomy. Receiver operator characteristic curves were calculated to assess predictive ability of AURKA and AURKB for pathologic response rates. Multivariable logistic regression models were used to assess the relationship of AURKA, AURKB, type of chemotherapy agent, and pathologic tumor stage with relapse and mortality events. 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). A standard predictive AURKA and AURKB tumor expression threshold has not been previously defined, so we analyzed the AURKA and AURKB percent tumor cell expression in quartiles. High expression was defined as the 75th quartile for each enzyme.

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 1. The median patient age in this cohort is 61 years (34−81). The majority (92%) of patients received a cisplatin-based NAC regimen. Thirteen (26%) patients achieved a pCR, and 22 (44%) patients were found to have residual pathologic muscle-invasive disease (ypT2-4) after NAC. The median duration of follow-up for this cohort is 2.5 years (0.4, 8.2). Sixteen (32%) patients have relapsed, and 19 (38%) patients have died. Patients who achieved a pCR following NAC demonstrated a trend toward improved RFS (HR 5.74, 95% CI = 0.76−43.6, $P = 0.09$) and OS (HR 2.03, 95% CI=0.59 −7.0, $P = 0.26$) compared to those who had pathologic residual disease (Fig. 1).

3.2. Aurora kinase A and B expression

AURKA and AURKB expression was detected in most specimens containing viable tumor cells (Fig. 2). The percentage of tumor cells expressing AURKA and AURKB were similar in diagnostic TURBT specimens (AURKA median 20% [1%−70%], AURKB median 22.5%, [5% −80%]). The threshold observed for the upper quartile of percent tumor cell expression of AURKA and AURKB in TURBT specimens was 25% and 40%, respectively. Baseline AURKA expression was similar in patients who achieved a pCR (median 20%, [2%−55%]) and who had residual muscle-invasive disease (median 15%, [2%−70%]). Seventeen (34%) patients had tumor expression of at least 1 aurora kinase isoform in the upper quartile, and tumors from 6 (12%) patients had coexpression of both AURKA and AURKB within the upper quartiles for this cohort.

3.3. Baseline AURKA and AURKB expression and pathologic response

Analysis of baseline AURKA and AURKB tumor expression in relation to pathologic response to NAC was performed. Neither baseline expression of AURKA (ROC 0.57, $P = 0.46$) nor AURKB (ROC 0.56, $P = 0.87$) predicted for pathologic residual muscle-invasive disease. Since this

Table 1
Patient characteristics

	Aurora kinase A		Aurora kinase B		All patients
	n		*n*		*n*(%)
	Hi	Lo	Hi	Lo	
	n = 12	*n* = 38	*n* = 11	*n* = 39	*n* = 50
Gender					
Male	11	27	6	32	38 (76)
Female	1	11	5	7	12 (24)
Perioperative chemotherapy					
MVAC[a]	3	16	2	17	19 (38)
Gemcitabine/Cisplatin	7	19	8	18	26 (52)
Other[b]	2	3	1	4	5 (10)
Relapsed?					
Yes	7	9	6	10	16 (32)
No	5	24	5	24	29 (58)
Other[c]	0	5	0	5	5 (10)
Deceased?					
Yes	10	9	7	12	19 (38)
No	2	27	4	25	29 (58)
Unknown	0	2	0	2	2 (4)
Clinical stage at diagnosis					
T1	0	2	0	2	2 (4)
T2	12	35	11	36	47 (94)
T4	0	1	0	1	1 (2)
N0	12	36	11	37	48 (96)
N1	0	2	0	2	2 (4)
Pathologic stage at cystectomy					
ypT0	3	10	2	11	13 (26)
ypTis-T1	3	12	3	12	15 (30)
ypT2-T4	6	16	6	16	22 (44)
ypTanyN+	2	6	1	7	8 (16)

[a] Methotrexate, vinblastine, adriamycin, cisplatin.
[b] Gemcitabine/carboplatin (4), cisplatin, methotrexate, vinblastine (1).
[c] Death in postoperative period (3), lost to follow-up (2).

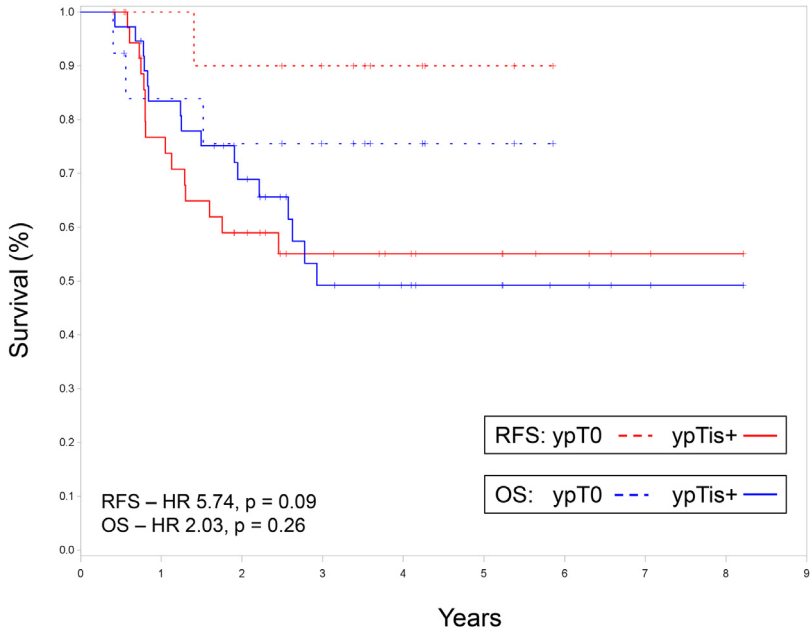

Fig. 1. Relapse-free and overall survival by pathologic response rate following neoadjuvant chemotherapy.

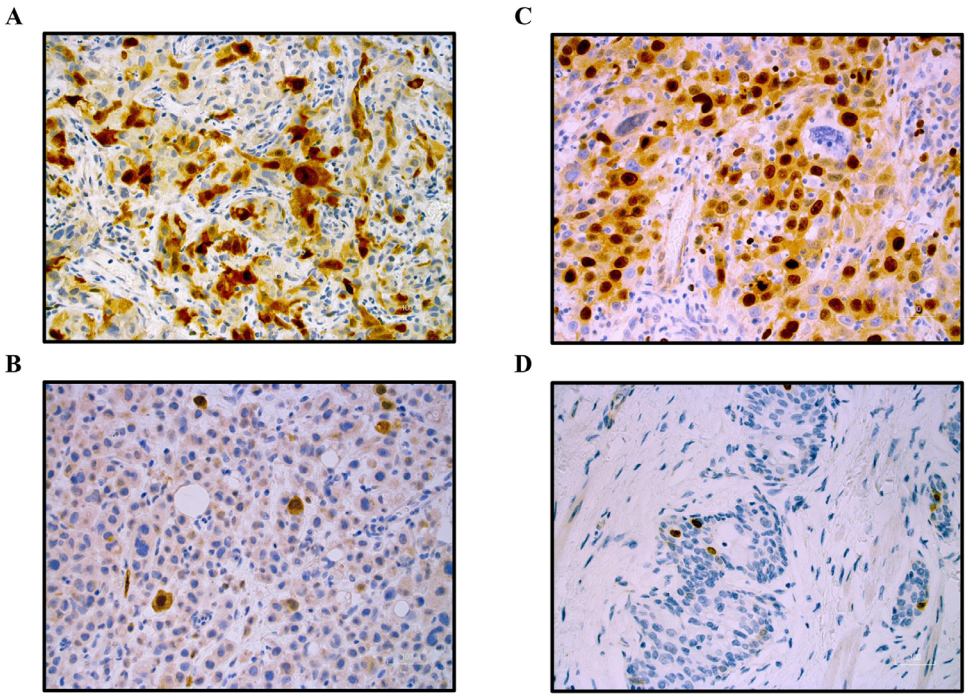

Fig. 2. Representative aurora kinase protein expression by immunohistochemistry in untreated primary tumor samples are shown. (A) aurora kinase A, high; (B) aurora kinase A, low; (C) aurora kinase B, high; (D) aurora kinase B, low.

finding was unexpected, we also assessed the impact of baseline aurora kinase expression on the likelihood of achieving a pCR to NAC and also did not observe a predictive relationship (AURKA ROC 0.53, $P = 0.64$; AURKB, ROC = 0.59, $P = 0.50$). Thus baseline AURKA and AURKB expression levels did not predict for pathologic stage following NAC in MIBC in this cohort.

3.4. Baseline AURKA and AURKB expression and survival

Prior studies had reported a negative prognostic value of AURKA expression on survival in patients with local bladder cancer. Thus we also examined the impact of AURKA and AURKB expression on RFS and OS in this cohort, since the prognostic value in patients treated with NAC has

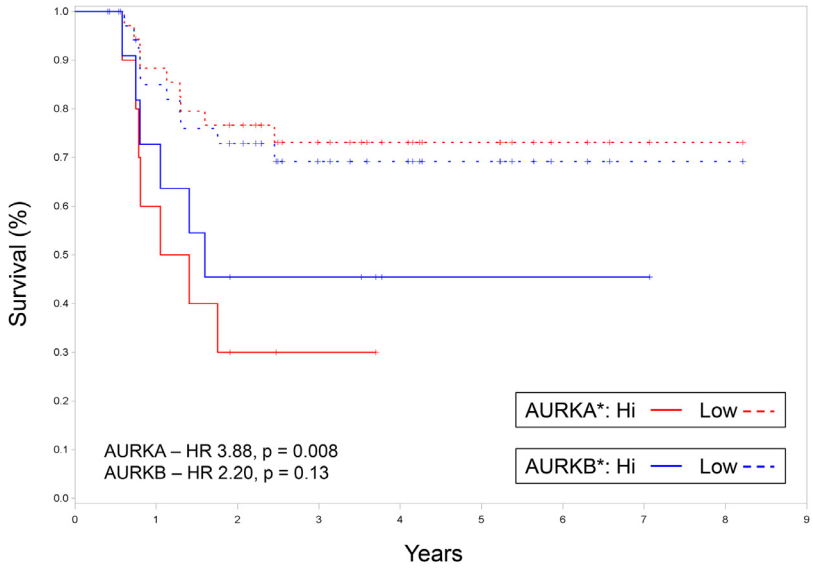

Fig. 3. Relapse-free survival according to baseline AURKA and AURKB expression. *High—expression within upper quartile expression, Low—expression within lower 3 quartiles.

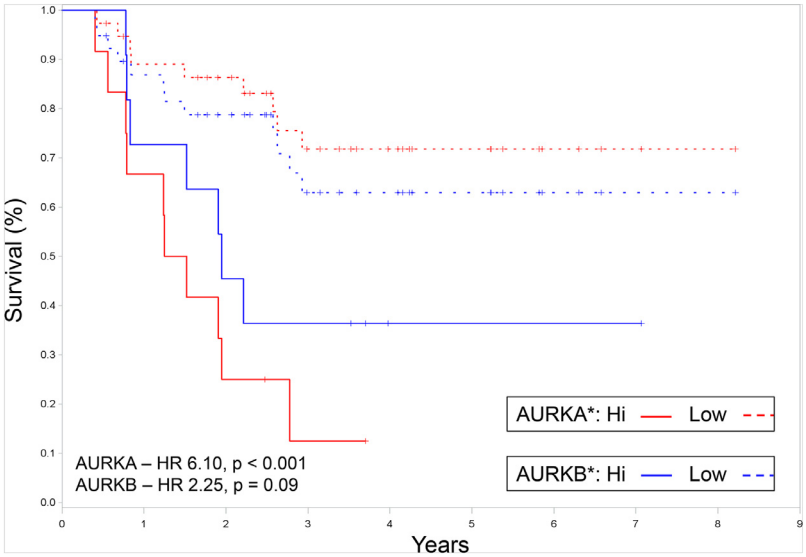

Fig. 4. Overall survival according to baseline AURKA and AURKB expression. *High—expression within upper quartile expression, Low—expression within lower 3 quartiles.

not been described. In univariate analysis, the median RFS for patients in the upper quartile of AURKA expression at baseline compared to the lower 3 quartiles was 11.2 vs. not reached (NR) months (HR 3.88, $P = 0.008$) (Fig. 3). We also observed that patients from the upper quartile of AURKA expression demonstrated an inferior OS compared to the lower 3 quartiles 16.7 vs. NR months (HR 6.10, $P < 0.001$) (Fig. 4). Using multivariable analysis for OS, both high baseline AURKA expression and pathologic residual muscle-invasive disease also predicted for inferior overall (data not shown).

Trends toward similar outcomes were observed with high baseline AURKB expression in univariable analysis, though did not reach statistical significance. Median RFS for patients in the upper quartile of AURKB expression at baseline was 19.2 vs. NR months (HR 2.2, $P = 0.13$) for patients in the lower 3 quartiles (Fig. 3). Patients from the upper quartile of AURKB expression also demonstrated an inferior OS compared to the lower 3 quartiles (23.4 vs. NR months, HR 2.25, $P = 0.09$) (Fig. 4).

3.5. Postchemotherapy AURKA and AURKB expression and clinical outcome

Aurora kinase protein expression in cystectomy specimens containing residual urothelial carcinoma was also measured to assess the impact of NAC on aurora kinase

expression and correlation with clinical outcomes. Cystectomy specimens with residual disease contained a modest decrease in tumor AURKA (median −5%, $P < 0.0001$) and AURKB (median −10%, $P < 0.0001$) protein expression levels compared to pretreatment TURBT specimens.

The potential correlation of post-NAC aurora kinase expression on survival outcomes was assessed. Change in tumor aurora kinase expression from pre-NAC TURBT to post-NAC cystectomy specimens did not predict for RFS or OS (data not shown). In post-NAC cystectomy specimens with residual disease, a modest negative correlation between OS and AURKB ($r = -0.36$, $P = 0.04$) but not AURKA ($r = -0.255$, $P = 0.14$) was observed. In this cohort, small patient numbers precluded definitive conclusions regarding the prognostic value of postchemotherapy tumor aurora kinase expression in patients with residual disease.

4. Discussion

The results of this study support the hypothesis that baseline tumor overexpression of AURKA or AURKB confers an adverse prognostic value in MIBC patients. To our knowledge, this dataset is the first to report an association between baseline AURKA and AURKB tumor expression and poor survival in a cohort that received neoadjuvant platinum-based chemotherapy. These findings identify AURKA and possibly AURKB as candidate biomarkers that may potentially identify MIBC patients unlikely to benefit from NAC based on the observed adverse prognostic value.

Although we did not observe a correlation between pathologic response rate and expression of aurora kinases A and B, this finding may be explained by the potential confounding effect of an incomplete TURBT prior to initiation of NAC or may reflect differential gene expression in primary and occult metastatic deposits, as we have previously demonstrated [23,24]. Documentation for all pretreatment TURBT procedures was not available to assess the rate of incomplete TURBTs in this cohort, so we cannot determine whether the extent of prechemotherapy TURBT may have influenced these results.

Our findings, however, add to the existing body of literature identifying aurora kinases as important prognostic markers and possible therapeutic targets for patients with locally advanced bladder cancer and raise several considerations. First, no standard prognostic or predictive threshold for high baseline AURKA or AURKB protein expression has yet been defined and should be a focus of future investigation. Second, existing datasets are retrospective in design, thus prospective investigation to establish the predictive value of baseline AURKA or AURKB expression for lack of chemotherapy benefit in MIBC is needed before these markers should be utilized to guide therapeutic decisions. Third, this study is the first to examine coexpression of AURKA and AURKB proteins in patients receiving NAC. Coexpression of AURKA and AURKB proteins was consistently observed in this cohort implying that future study of aurora kinases in urothelial carcinoma should include concurrent assessment of both isoforms. Fourth, we did not measure expression of the third known isoform, aurora kinase C [25], in this study due to the lack of an available diagnostic antibody at the study outset. Whether aurora kinase C also contributes to the biology of urothelial carcinoma remains unknown and should be considered in future studies.

Alisertib, a selective aurora kinase A inhibitor, failed to show meaningful clinically activity as monotherapy in an unselected population of patients with advanced urothelial carcinoma [13]. The investigators identified a polymorphism in the AURKA gene that may have predicted for improved progression-free survival; however, AURKA protein expression levels were consistently high (>70%) in most biopsy specimens in this study and did not correlate with outcome [13, 26]. We utilized a different AURKA antibody for our study and observed lower AURKA tumor expression rates than reported in this prior study. The variation in AURKA expression rates between these 2 studies could be explained by either differential AURKA antibody specificities or increased tumor expression of AURKA in the metastatic setting.

Future study of aurora kinase inhibitors in urothelial carcinoma may benefit from concurrent assessment of pan-aurora kinase levels to determine potential confounding effect of isoform coexpression and investigation of the potential discordance in aurora kinase expression between primary and metastatic lesions. Also, further testing of aurora kinase inhibitors in combination with cytotoxic chemotherapy may improve the likelihood of therapeutic benefit, since preclinical data have consistently demonstrated synergistic antitumor effects when combining aurora kinase inhibitors with traditional cytotoxic agents such as cisplatin.

5. Conclusions

Our findings support the hypothesis that overexpression of AURKA and possibly AURKB identifies MIBC patients with poor prognosis despite the use of NAC and validate the aurora kinases as potential therapeutic targets in urothelial carcinoma. Furthermore, investigation of unselective aurora kinase inhibitors in combination with NAC should be explored for the potential to enhance chemotherapy-induced cytotoxicity. Prospective study of the predictive value of high AURKA and AURKB expression in MIBC should be pursued to determine whether these markers could be used to select patients with MIBC unlikely to benefit from NAC and who should be considered for alternate therapeutic strategies.

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