Genomic Predictors of Response to Neoadjuvant Cisplatin-based Chemotherapy in Upper Tract Urothelial Carcinoma (UTUC)

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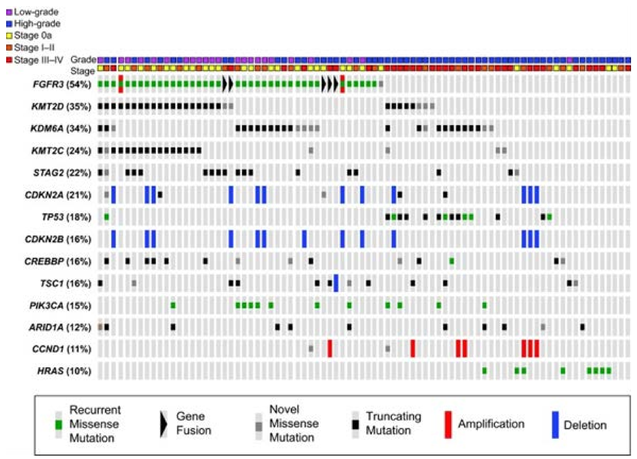
Introduction

- Use of neoadjuvant cisplatin-based chemotherapy (NAC) in UTUC is based on evidence of survival benefit in urothelial carcinoma (UC) of the bladder.
- However, concerns regarding toxicity and lack of efficacy have prevented its widespread adoption.
- We aim to analyze the genomic profiling data of UTUCs from patients who received NAC to identify predictors of chemo-sensitivity.

Methods

- We reviewed data on all ≥cT2anyNM0 high-grade UTUC patients who underwent genomic profiling prior to cisplatin-based NAC.
- We evaluated 14 of the most commonly altered genes in UTUC (≥10%) identified by the MSK-IMPACT assay in a recently published study (FGFR3, KMT2D, KDM6A, KMT2C, STAG2, CDKN2A, TP53, CDKN2B, CREBBP, TSC1, PIK3CA, ARID1A, CCND1 and, HRAS), Figure1. We also looked at ERCC2 and Bcl-2, which have been linked with response to chemotherapy in bladder UC.
- We assessed the association between alterations and pathologic response (<pT2 at Radical nephroureterectomy) using univariate logistic regression.

Fig. 1 Representation of the 14 most frequently altered genes in a series of upper tract urothelial carcinoma tumors (Sfakianos JP et al. Eur Urol. 2015).



Results

Mutation	Responders (n=16)	Non-responders (n=6)
CCND1 amplification	1 (6.2%)	2 (33.3%)

- 62 (9.1%) received cisplatin-based NAC and 22 underwent MSK-IMPACT sequencing of pre-treatment tumor tissue.
- Of these patients, 16 (73%; 95% CI 50%, 89%) achieved <pT2 response to NAC, Table 1.
- Three patients had CCND1 amplification, one of whom had pathological NAC response. CCND1 amplification was associated with non-significant lower odds of NAC response on pathology (OR 0.13; 95% CI 0.01, 1.87).
- 15/19 (79%) patients without CCND1 amplification had NAC response on pathology compared to 1/3 (33%) patients with CCND1 amplification had NAC response on pathology (difference 46%, 95%CI -11%, 100%).

Table 1 Patient and tumor characteristics of those who had IMPACT testing, stratified on chemotherapy response on pathology (N=22)

	Responders (N=16; 73%)	Non-responders (N=6; 27%)
Age at Surgery	64 (53, 70)	66 (63, 71)
Male	8 (50%)	3 (50%)
Smoking Status		
Never	6 (38%)	2 (33%)
Former	10 (63%)	2 (33%)
Current	0 (0%)	2 (33%)
Number of Cisplatin Cycles	5 (4, 8)	4 (4, 4)
Clinical Primary Tumor Stage		
T2	15 (94%)	4 (67%)
T3	1 (6.3%)	1 (17%)
T4	0 (0%)	1 (17%)
Clinical Regional lymph nodes Stage		
N0	13 (81%)	4 (67%)
N1	1 (6.3%)	2 (33%)
N2	2 (13%)	0 (0%)
Hydronephrosis	9 (56%)	2 (33%)
Tumor Location in the Ureter (vs Kidney)	5 (31%)	1 (17%)
Multifocal Tumor (vs Unifocal)	11 (69%)	4 (67%)
Positive Surgical Margin	0 (0%)	0 (0%)
Unknown	1 (6.3%)	0 (0%)
Lymph Node Dissection	16 (100%)	4 (67%)
Number of Nodes Removed on LND	17 (8, 26)	25 (21, 29)
Number of Positive Nodes Removed on LND	0 (0, 0)	0 (0, 1)

Conclusions

- CCND1 amplification was found to be non-significantly associated with lack of response following cisplatin-based NAC.
- Similar findings in cancers of the head and neck, colon, breast and bladder suggest the importance of CCND1 as a prognostic marker and potential actionable target in cisplatin-resistant high risk UTUC; however, larger studies are needed for confirmation.