Utility of circulating tumor DNA and transcriptomic profiling in predicting outcome in muscle invasive bladder cancer patients

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Background & objectives

Localized muscle invasive bladder cancer (MIBC) is treated with neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC); however, only 40-50% respond to NAC and 50% experience relapse.

Evaluation of treatment efficacy and early detection of relapse are major clinical challenges.

Methods

Cohort [1]: NAC prior to RC (n=68, median follow-up (FU) 58 months, Christensen et al. JCO 2019); cohort [2]: no NAC, RC only (n=120, median FU 71 months). Circulating tumor DNA (ctDNA) was analyzed before NAC (n=63), prior to RC ([1] n=67; [2] n=115) and after RC ([1] n=66; [2] n=37) using Signatera™. RNA-seq was performed on 176 tumors.

Results

Updated clinical FU for cohort [1] showed that ctDNA-positive patients had significantly worse recurrence-free survival (RFS) compared to ctDNA-negative patients (before NAC: HR=16, 95%CI=3.6-70.5, p=0.0002; during surveillance after RC: HR=27.6, 95%CI=7.9-96.9, p<0.0001). After NAC prior to RC, 84% (52/62) of patients were ctDNA-negative, and of these 81% (42/52) achieved pathological complete response (pCR), while none of the ctDNA-

positive patients achieved pCR (PPV 100%; NPV 81%). For the no-NAC cohort, presence of ctDNA was also prognostic at both time points (before RC: HR=2.5, 95%CI=1.4-4.4, p=0.001; single time point after RC: HR=10.1, 95%CI=3.2-31.6, p<0.0001). Transcriptomic pathway analysis showed an enrichment of oncogenic pathways, namely EMT and hypoxia (q<0.0001), in tumors from ctDNA-positive patients (n=62/142), potentially reflecting a more aggressive phenotype of ctDNA shedding tumors. After NAC, enrichment of EMT (q<0.0001) and TGF-β signaling (q=0.005) was found in ctDNA-positive patients (n=7) while anti-tumor immune pathways, including IFNα and IFNγ response (q=0.03 and q=0.04) were seen in patients with ctDNA clearance (n=11). IFNα and IFNγ response pathways were upregulated in ctDNA-negative patients without relapse in cohort [2] (q<0.0001, n=34/57). Classification according to the MIBC consensus classes identified more Ba/Sq tumors among the ctDNA-positive patients (p<0.0001). The potential clinical benefit of NAC in ctDNA-positive and -negative patients is under investigation.

Conclusion

Presence of ctDNA was associated with worse prognosis for both NAC and no-NAC treated patients. Transcriptomic analysis of primary tumors showed that anti-tumor immune responses may be associated with a particularly good outcome whereas EMT may be promoting more aggressive disease.