Biomarker investigation using ctDNA in patients treated with sorafenib for advanced HCC

[1]서울아산병원 내과, [2]서울아산병원 종양내과, [3]국립암센터 진단검사의학과, [4]국립암센터, [5]건국대학교 수의과대학, [6]녹십자

*오충렬[1], 박숙련[2], 공선영[3], 김민경[4], 윤경아[5], 조은해[6], 장자현[6], 이준남[6], 류백렬[2]

Background: The aim of this study was to explore potential biomarkers in patients treated with sorafenib for advanced hepatocellular carcinoma (HCC) using circulating tumor DNA (ctDNA). **Methods:** We identified 184 patients who had started sorafenib therapy between March 2014 and November 2016 from a prospective biomarker cohort of Asan Medical Center. With blood samples collected before initiation of sorafenib, ctDNA concentration of each patient was quantified. We then applied low depth whole genome sequencing from ctDNA to find copy number aberrations in HCC and employed Q-score, defined as a standard deviation regarding Z-scores of sequenced reads on each chromosome. **Results:** Of 184 patients, 151 were finally included in the analysis. 96 patients achieved partial response, stable disease or non-CR/non-PD with sorafenib therapy (non-PD group) whereas 55 exhibited progressive disease (PD group). The concentration of ctDNA in PD group was significantly higher than that in non-PD group (0.82 vs. 0.63 ng/uL; $p=0.006$). The PD group had also higher level of Q-score than the non-PD group (6.68 vs. 3.82; $p=0.031$). Median duration of time to progression (TTP) was 3.22 months and overall survival (OS) was 7.59 months for 151 patients. Divided into two groups according to the median value of ctDNA level, patients with high ctDNA had significantly worse TTP (median, 2.17 vs. 4.11 months; $p=0.002$) and OS (median, 4.11 vs. 14.8 months; $p<0.001$) than those with low ctDNA. Likewise, patients with higher Q-score than median value had significantly shorter TTP (median, 2.33 vs. 4.04 months; $p=0.004$) and OS (median, 4.67 vs. 14.8 months; $p<0.001$) compared to those with lower Q-score. After adjusting confounding factors including baseline alpha-fetoprotein level or presence of vascular invasion, by multivariate Cox regression analysis, the ctDNA level and Q-score remained independent prognostic factors associated with both TTP ($p=0.012$ and 0.022, respectively) and OS ($p<0.001$, respectively). **Conclusions:** Our results demonstrated that the concentration of ctDNA and copy number aberrations represented by Q-score could be candidate prognostic biomarkers in patients treated with sorafenib for advanced HCC.

Changes in PD-L1 expression by cisplatin treatment in head and neck squamous cell carcinoma

[1]서울대학교병원 내과, [2]서울대학교병원 병리과, [3]서울대학교 의과대학 암연구소, [4]서울대학교병원 이비인후과, [5]서울대학교병원 방사선종양학과

*옥찬영[1], 김세희[2], 김범석[1,3], 김소연[3], 안용운[3], 정은재[4], 김진호[5], 김태민[1,3], 권성근[4], 전윤경[2], 정경천[2], 김동완[1,3], 우홍균[5], 성명훈[4], 허대석[1,3]

Programmed death-ligand 1 (PD-L1) expression has been suggested to be a predictive marker for anti-PD-1/PD-L1 therapy. We hypothesized that PD-L1 expression would be changed during treatment in head and neck squamous cell carcinoma (HNSCC). We reviewed clinical information of HNSCC patients who were treated at Seoul National University Hospital 2004-2012. Paired HNSCC tissues prior to and after treatment were evaluated for PD-L1 protein expression by immunohistochemistry. PD-L1 positivity was defined by weak, moderate, or strong staining in ≥ 5% of tumor cells. **Results:** showed that PD-L1 expression status changed after treatment in 37.1% (13/35) of HNSCC patient samples. Among the 13 patients whose baseline PD-L1 was negative, PD-L1 expression was increased in 9 cases (69.2%) and remained negative in 4 cases (30.8%, $p=0.003$). Patients exposed to cisplatin had a tendency to show high PD-L1 up-regulation (83.3%, $p=0.037$) compared to those not exposed to cisplatin (57.1%, $p=0.072$). To validate these findings in vitro, changes in PD-L1 expression in HNSCC cell lines (Detroit-562, PCI-13, SNU-1041, SNU-1066, SNU-1076, and FaDu) were analyzed by western blotting and flow cytometry after treatment with cisplatin and interferon-gamma. PD-L1 expression was significantly up-regulated after cisplatin, along with phosphor-MAP/ERK up-regulation In HNSCC cell lines. In conclusion, PD-L1 expression in HNSCC may be altered during cisplatin treatment, activating the MAPK/ERK kinase pathway.