Selecting Patients with Stage II or III Colorectal Cancer for 5-Fluorouracil-based Adjuvant Chemotherapy Using Proteomic Analysis

Hong Yan1, Ji Hyung Hong2, Hee Yoon Lee2, Jae Ho Byun2, Fabiola Cecchi1, Yuan Tian1, Sant Schwartz2, Eunkyung An1, Todd A. Hembrough1

1 NantOmnics, LLC, USA; 2 Department of Internal Medicine, Incheon St. Mary’s Hospital, Incheon, Korea

BACKGROUND

- 5-fluorouracil (5-FU) is widely used to treat high-risk stage II and III colorectal cancer (CRC). Even in combination with oxaliplatin, about 15% of stage II patients and 30% of stage III patients relapse within 48 months [1]. Identifying biomarkers of response to 5-FU can improve patient selection for chemotherapy.
- 5-FU requires biochemical conversions to mediate cytotoxicity. This process involves enzymes such as thymidine phosphorylase (TYP) and uridine-cytidine kinase 2 (UCK2).
- Mass spectrometry-based targeted proteomic analysis objectively quantitates candidate protein biomarkers in formalin-fixed, paraffin-embedded (FFPE) tumor samples.
- Protein expression levels of TYP were associated with overall survival in a retrospective analysis of gastric cancer patients who received 5-FU-based chemotherapy [2].
- We hypothesized that protein biomarkers associated with 5-FU metabolism predict survival in stage III CRC patients treated with 5-FU.

METHODS

RESULTS

Figure 2. Distribution of UCK2 protein expression in stage III CRC (n=128). The dashed line denotes the cutoff of 319 attomoles per microliter (amol/μL).

Stage III CRC: 5-FU-treated patients with high UCK2 expression had longer RFS and OS

CONCLUSIONS

- Stage III CRC patients with high intratumoral expression of UCK2 (>319 amol/μL) derived significantly more survival benefit from 5-FU-based chemotherapy, compared with low UCK2 expressors. The association between UCK2 level and survival remains statistically significant in the stage III subgroup.
- Stage III CRC patients with a signature of high TYP and high UCK2 expression gained the largest survival benefit from 5-FU.
- Quantitative targeted proteomics represents an objective and robust approach to identifying likely responders to 5-FU-based chemotherapy.

FUTURE DIRECTION

- Studies are underway to validate UCK2 and TYP as predictive biomarkers for 5-FU-based chemotherapy.

REFERENCE


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Figure 1. In archived clinical samples of stage III CRC (n=128), 66 proteins were quantified with mass spectrometry. Protein expression cutoffs were derived via Cox proportional hazard modeling and Monte-Carlo 2-fold cross-validation. Patients were dichotomized by UCK2 and TYP protein expression level. Survival curves were compared using the Mantel-Cox log-rank test.

Figure 3. (A) Among stage III CRC patients receiving 5-FU (n=128), those with UCK2<319 amol/μL (n=104) had longer relapse-free survival (RFS) compared with patients with lower UCK2 expression (hazard ratio [HR]: 0.45; p=0.0134; median RFS not reached vs. 1517 days). (B) High UCK2 expression was similarly associated with superior overall survival (OS) (HR: 0.3; p=0.0033; median OS [mOS] not reached vs. 1736 days). The associations between UCK2 level and survival remained significant in bivariate Cox models after adjusting for clinical covariates, except for differentiation status.

Stage III CRC: 5-FU-treated patients with high levels of TYP and UCK2 had longer RFS and OS

Figure 4. (A) Among stage III CRC patients receiving 5-FU (n=107), those with UCK2<319 amol/μL (n=87) had longer RFS compared with patients with lower UCK2 expression (HR: 0.38; p=0.0031; mRFS not reached vs. 778 days). (B) High UCK2 expression was similarly associated with longer OS (HR: 0.3; p=0.0012; mOS not reached vs. 1736 days).

Figure 5. (A) Patients with high levels of both TYP and UCK2 (n=23) had longer RFS than patients with low TYP and UCK2 expression (n=23; mRFS not reached vs. 1517 days) and others (n=85). (B) High levels of TYP and UCK2 were similarly associated with longer OS than low levels of TYP and UCK2 (mOS not reached vs. 1736 days). The p values were calculated with ANOVA.

CONCLUSIONS

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- Stage III CRC patients with a signature of high TYP and high UCK2 expression gained the largest survival benefit from 5-FU.
- Quantitative targeted proteomics represents an objective and robust approach to identifying likely responders to 5-FU-based chemotherapy.