Expression of cholinesterase is associated with prognosis and response to chemotherapy in advanced gastric cancer

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Background: Cholinesterase (CHE) as a routine serum biomarker in gastric cancer (GC). However, little research has been done on its clinical value in advanced GC. In addition, it is not clear whether it can be used as biomarker for the response and prognosis of advanced GC patients.

Methods: Between Jan. 2013 and Dec. 2016, a total of 150 patients with advanced GC treated with first-line chemotherapy were admitted to Changzhou Tumor Hospital Affiliated to Soochow University. We retrospectively identified serum CHE level before chemotherapy and abstracted clinicopathologic features and treatment outcomes. Univariate and multivariate survival analyses were performed to assess the relationship between serum CHE levels and progression-free survival (PFS) and overall survival (OS). Descriptive statistics were used to correlate level of CHE state and clinicopathological parameters.

Results: A total of 150 advanced GC patients were included and divided into positive and negative CHE values. CHE negative was associated with significant poorer progression-free survival (HR, 1.60; 95% CI, 1.141-2.243; P = 0.006), poorer overall survival (HR, 1.76; 95% CI, 1.228-2.515; P = 0.002) and trend of poorer response (HR, 0.56; 95% CI, 0.272-1.129; P = 0.104). The correlations were significant in multivariate analysis including PS score (P < 0.05). CHE positive was detectable in 93 of 150 (62%) post-chemotherapy samples which was associated with a superior survival outcome compared with patients in whom CHE became negative after chemotherapy.

Conclusions: Cholinesterase negative in the serum of advanced GC was significantly associated with poor PFS and OS. The results suggested that CHE analysis before chemotherapy was a promising prognostic marker for advanced GC. A post-chemotherapy CHE analysis may define a subset of patients who are still at high risk of becoming CHE negative even if they are CHE positive before chemotherapy. This high-risk group offers a unique opportunity to explore novel treatments.

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Computing HRD score by a capture-based NGS panel reveal its prevalence in Chinese breast, ovarian, prostate and pancreatic cancer patients

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Background: Previous studies have shown the treatment indication for poly(ADP-ribose) polymerase inhibitors could expand to patients with instable genome, characterized by homologous recombination deficiency (HRD) status beyond those with BRCA mutations (NOVA trials, ARIEL2/3 trials and QUADRA trials). Recent studies showed that pancreatic and prostate cancer patients with BRCA mutations could also benefit from PARPi treatment. Therefore, evaluating HRD status in Breast, Ovarian, Prostate and Pancreatic cancers could reveal additional cases who may potentially benefit from this novel target therapy.

Methods: We developed an HRD score algorithm, termed as 3DmedHRD, to characterize genomic instability of tumors using over 10000 SNPs. It combines three classical factors, including loss of heterozygosity score (LOH), telomeric allelic imbalance score (TAI), large-scale state transition score (LST), along with an optimized tumor ploidy and purity prediction algorithm. The method was trained using 45 BRCA-deficient and 25 BRCA-intact tumor samples. HRD score cutoff was determined to achieve 95% sensitivity. BRCA-deficiency was defined to possess deleterious germline or somatic mutation in BRCA1 or BRCA2, with loss of second allele by LOH in the affected gene. The cutoff was subsequently evaluated by an independent cohort to demonstrate similar performance. We then applied the model to characterize the population frequency of HRD positivity across tumor types using samples collected in a local LDT lab in Shanghai.

Results: The observed frequency of patients with deleterious BRCA 1/2 mutation are 10.4%, 21.6%, 5.1% and 4.1% for Breast (n = 1106), Ovarian (n = 134), Prostate (n = 59), Pancreatic cancers (n = 270) respectively. The corresponding percentage of HRD positive cases in BRCA wildtype patients are 38.7%, 35.1%, 10.2% , 5.6%. When considering patients with either BRCA1/2 mutations or positive HRD status, the population frequencies are 49.1%, 56.7%, 15.3%, 9.6%.

Conclusions: We here report the development of the 3DmedHRD score as a biomarker to quantify the “genomic scar” of tumor tissues. A retrospective analysis of over 500 cases first time revealed HRD population frequencies in a Chinese cohort.

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