Review Article
Personalized and dynamic therapy for gastric cancer: a perspective

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Abstract: Genomic studies have provided key insights into how cancers develop, evolve, metastasize, recurrence and respond to treatment. The advance of liquid biopsy using circulating tumor DNA (ctDNA), the next-generation sequencing (NGS) and bioinformatics has led to an unprecedented view of the cancer genome and its evolution, and made the dynamic monitoring of recurrence and selective evolution of cancer during therapy a reality. Here we illustrate a proposed strategy of personalized and dynamic therapy for gastric cancer based on the technologies of ctDNA and NGS. The goal of this strategy is to realize personalized and dynamic systemic therapy for gastric cancer and improve patients' outcomes.

Keywords: Circulating tumor DNA, next-generation sequencing, personalized cancer therapy, dynamic therapy

Introduction

Repeated biopsies of tumors during the course of treatment are crucial for the improved understanding and monitoring of changes in tumor cell populations during disease progression and in response to therapies. However, repeated biopsies of tumor tissue involve invasive procedures and tumor heterogeneity will confound interpretation of analyses. The ability to investigate solid tumor through noninvasive sampling of blood is one of the most exciting and rapidly advancing fields in cancer diagnostics. Analysis of circulating tumor DNA (ctDNA) derived from different metastatic sites may provide a more comprehensive picture than the analysis of a single metastatic lesion. The application of next-generation sequencing (NGS) together with advanced computational methods has recently allowed ctDNA-based tumor genotyping. These advanced noninvasive diagnostic capabilities and their applications in guiding precision cancer therapies are poised to change the ways in which we select and monitor gastric cancer therapy.

Combination of liquid biopsy and next-generation sequencing

Circulating tumor DNA (ctDNA) enters the circulation following apoptosis and/or necrosis of tumor cells and is typically fragmented to around 160-180 bp reflecting the degradation of DNA into nucleosomal units which is characteristic of the apoptotic process [1, 2].

ctDNA from blood samples necessitated repeated sampling of cancer-derived materials to adjust therapy in response to tumor evolution under selective pressure. ctDNA can be detected in a range of different solid malignancies and levels have been shown to increase with disease stage. DNA7. It was reported that mutations present in ctDNA are highly concordant with those present in the matched tumor [2-6]. It was also reported that enumeration of ctDNA amounts can allow dynamic changes in tumor burden to be accurately tracked over time [2, 4]. ctDNA has a superior sensitivity to other circulating biomarkers and a dynamic range that correlates with tumor burden [7].
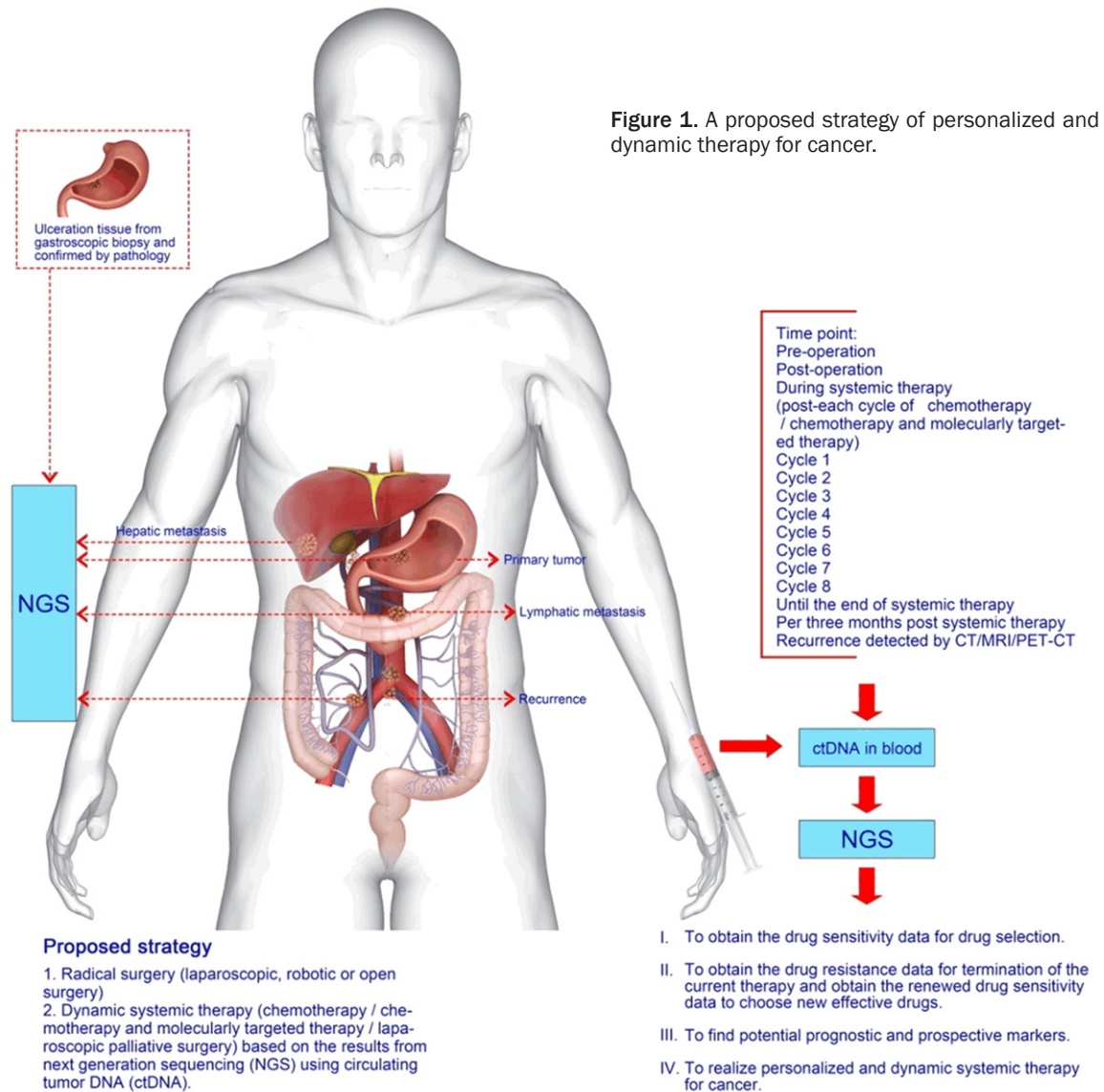
Figure 1. A proposed strategy of personalized and dynamic therapy for cancer.

ctDNA offers a relatively easy and noninvasive method for the analysis of primary, metastatic and recurrent tumors. Numerous studies demonstrated the utility of monitoring the patients' blood for ctDNA to detect cancer progress, evolution, or resistance to therapy [1-5, 8-19].

The analysis of ctDNA is challenging and requires highly sensitive techniques due to the small fraction of tumor specific DNA present within background levels of normal cell-free DNA (cfDNA). Recent advances in genomics technologies are now providing new opportunities for the analysis of ctDNA. NGS technologies are now being applied to plasma DNA analysis to allow more comprehensive detection of mutations across wider genomic regions. Advances in NGS have made it possible to precisely characterize all somatic coding mutations that occur during the development and progression of individual cancers. Whole-genome sequencing (WGS) has now been directly applied to plasma DNA analysis, to provide an unprecedented view of somatic chromosomal alterations and copy number aberrations in ctDNA genome-wide [20, 21]. NGS of ctDNA has been demonstrated to be an effective non-invasive tool for monitoring tumor burden, evolution, therapeutic responses and resistance to therapy [2-5, 9-18]. Numerous studies have also demonstrated that ctDNA analysis can allow the emergence of mutations

associated with treatment resistance to be assessed noninvasively from plasma DNA [6, 8, 10, 22, 23].

Monitoring tumor burden and treatment response is important in all phases of cancer management to avoid continuing ineffective therapies, to prevent unnecessary side-effects and to determine the benefit of new therapeutics. The combination of ctDNA and NGS facilitated the oncologists to investigate cancer to a new level, the dynamic genetic level.

Heterogeneity between primary tumors, corresponding metastatic tumors, and recurrent tumors

Over the past few years, genomic studies have demonstrated intratumor heterogeneity and heterogeneity in primary tumors, corresponding metastatic and recurrent tumors as recognized characteristics of solid tumors [6, 12, 13, 16, 17, 24-40]. These genomic differences may affect the clinical outcome of anticancer therapy. A retrospective study investigated the role of PTEN loss, AKT phosphorylation and KRAS mutations in primary colorectal tumors and their corresponding metastases on the activity of cetuximab plus irinotecan, which gave us direct evidence to reveal that the genetic heterogeneity in primary colorectal tumors and their corresponding metastases have different responses to EGFR-targeted therapy [41]. Studies of glioma recurrences found that the driver mutation landscapes were often significantly different from the initially detected driver mutations, suggesting that clones initiating recurrences had branched off early in tumor evolutionary histories [12]. Morrissy AS, et al. demonstrated the heterogeneity between primary tumor and recurrent tumor [13]. These studies indicated that molecularly targeted therapy is unlikely to be effective when the target is absent in the metastatic or recurrent tumors. In certain contexts, continued therapy in absent of target might accelerate tumor progression [42].

Natural evolution during cancer progress and selective evolution during cancer therapy

Cancer is a disease characterized by Darwinian evolution [43, 44]. Clones evolve dynamically in space and time underpinning important emergent features such as metastasis, drug resistance and recurrence [6, 16, 25, 31, 32, 34, 35]. Advances in NGS and bioinformatics have led to an unprecedented view of the cancer genome and its evolution. An overwhelming body of evidence has been collected demonstrating that cancers evolve during progression and therapy [10, 43, 45-47]. Therapy represents a very defined and stringent selection pressure during the evolution of a cancer, and several studies have now traced the clonal evolution of tumors during the course of treatment [12, 34, 48-51].

Natural and selective evolution of cancer is likely to have important consequences in clinical practice and novel techniques to obtain representative samples for genetic analyses, especially from metastatic and recurrent disease, are urgently needed to understand the clonal dynamics of evolving tumors through course of disease and therapy.

Hypothesis and perspective

Given these advances and the scientific data mentioned above, here we hypothesize and illustrate a proposed strategy of personalized and dynamic therapy for cancer (**Figure 1**). As shown in **Figure 1**, we choose gastric cancer as an example to illustrate the personalized and dynamic therapy strategy. In this strategy, radical surgery will be firstly performed when a gastric cancer is pathologically confirmed, following the dynamic therapy such as chemotherapy, chemotherapy in combination with molecularly targeted therapy, or laparoscopic palliative surgery based on the results from NGS using ctDNA and imaging technologies such as CT, MRI or PET-CT. The ctDNA in blood during the progress of therapy was obtained and analyzed using NGS. The goals of this strategy are: to obtain the drug sensitivity data for drug selection; to obtain the drug resistance data for termination of the current ineffective therapies and obtain the renewed drug sensitivity data to choose new effective drugs; to find potential predictive and prognostic markers; to realize early detection of cancer and detection of minimal residual disease, to monitor the evolution of molecular resistance, and finally to realize personalized and dynamic systemic therapy for cancer and improve patients outcomes.

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Disclosure of conflict of interest

None.

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