Expert Review of Gastroenterology & Hepatology

ISSN: 1747-4124 (Print) 1747-4132 (Online) Journal homepage: informahealthcare.com/journals/ierh20

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To cite this article: Georgios D Lianos, Alberto Mangano, William C Cho & Dimitrios H Roukos (2015) From standard to new genome-based therapy of gastric cancer, Expert Review of Gastroenterology & Hepatology, 9:8, 1023-1026, DOI: 10.1586/17474124.2015.1060856

To link to this article: https://doi.org/10.1586/17474124.2015.1060856

Published online: 24 Jun 2015.

From standard to new genome-based therapy of gastric cancer

Expert Rev. Gastroenterol. Hepatol. 9(8), 1023–1026 (2015)

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Randomized trials and meta-analyses have established surgery, radiotherapy, chemotherapy and targeted therapy in the multidisciplinary treatment of gastric cancer. However, personalized prediction of both therapeutic resistance and recurrence or metastatic disease progression still remains a researcher's dream. In this editorial, we summarize standard treatment approaches as well as their limitations, with an effort to highlight novel, next-generation sequencing technology-based clinical approaches for gastric cancer treatment.

Gastric cancer is an aggressive disease and still remains the fourth most common type of cancer and the second leading cause of cancer-related death around the world [1]. Gastric cancer, despite its declined incidence, accounts for an important proportion of cancer mortality. The incidence of gastric cancer appears to vary across geography, ethnicity and gender. Complete surgical resection (R0) represents undoubtedly the only potentially curative treatment. Moreover, despite optimization of surgery, standardization of radiotherapy and chemotherapy, the 5-year survival rate has moderately improved [2]. Particularly in advanced disease (stage III, IV) progress is too slow. In this way, there is now a crucial need to develop novel therapies for this complex, highly heterogeneous, aggressive and enigmatic type of cancer. Understanding the genetic background of gastric cancer will offer crucial insights into its pathogenesis and will help to identify novel biomarkers and treatment agents, shaping the way for the development of personalized therapeutic strategies in the near future [3].

Established therapy for gastric cancer

According to current guidelines, endoscopic mucosal resection is recommended for early gastric cancers (Tis or T1a tumors). Notably, surgery is recommended for T1b–2 stage or higher and any N stage. Curative gastrectomy is recommended for T1b–3 tumors, while T4 tumors require more extended resection. In addition, D2 lymphadenectomy has been the standard surgical therapeutic treatment for curable gastric cancer in East for many years, while in western countries, D2 lymphadenectomy only recently became a recommended surgical therapeutic option [4]. Moreover, in adjuvant chemotherapy field, S-1 is recommended in Japan in patients with stage II or III gastric cancer following D2 gastrectomy. In the ACTS-GC trial, S-1 patients demonstrated significantly better survival than those undergoing surgery alone [5]. National Comprehensive Cancer Network (NCCN) recommends, in accordance with the results of the MAGIC trial, perioperative chemotherapy with epirubicin, cisplatin and fluorouracil regimen for patients with locally advanced disease (T2 or higher and any N tumors) in the West [6]. Furthermore, based on the results of the CLASSIC trial in the east, postoperative chemotherapy is included with capecitabine and oxaliplatin after D2 gastrectomy in patients with T3, T4 and any N tumor [4,6]. For metastatic (M1) or unresectable tumors, doxetacel, cisplatin and fluorouracil regimen is recommended by NCCN, while in Japan the S-1 plus cisplatin regimen is used for these patients [6].

Keywords: cancer biomarkers • gastric cancer • genome-based therapy • next-generation sequencing analyses • personalized cancer medicine • whole-exome sequencing • whole-genome sequencing

EXPERT REVIEWS

 10.1586/17474124.2015.1060856 ISSN 1747-4124

Taken together, the above-mentioned, multimodal treatment of resectable gastric cancer has been standardized including R0-D2 gastrectomy and adjuvant treatment [4]. For advanced gastric cancer, several targeted molecular agents have been evaluated in randomized trials. The most important is represented by the monoclonal antibody trastuzumab, which has shown important antitumor activity against human epidermal growth factor receptor (HER)2-positive advanced gastric cancer. Recently, it has been established that the HER2-positive group of gastric cancer patients benefits from therapy with trastuzumab [7]. However, the major problem is the resistance to therapy. Although trastuzumab is a crucial anticancer drug, therapeutic resistance of breast cancer to trastuzumab represents a major problem. However, it is unclear whether similar mechanisms of therapeutic resistance are involved in gastric cancer. The crucial point is that resistance to trastuzumab has become a major problem and new strategies to overcome this resistance are needed. A high rate of advanced HER2-positive gastric cancer patients who presents therapeutic resistance on trastuzumab are candidates for second-line treatment.

It has to be highlighted that nowadays a new agent, trastuzumab-emtansine (T-DM1), provides important therapeutic efficacy in HER2-positive breast cancer patients. The big hope is that similar results will be reached also in HER2-positive gastric cancer patients. There is a need for randomized controlled trials in order to evaluate the therapeutic efficacy of T-DMI in gastric cancer patients. Moreover, we have also highlighted that immune-related therapies have presented important efficacy in different tumor types. A very promising agent is represented by programmed death 1-blocking agent, including pembrolizumab. The major hope is that these immune therapies will overcome mechanisms of resistance also in gastric cancer setting.

Limitations of therapeutic resistance

Many patients, even after a complete gastric cancer resection (R0) and adjuvant treatment, experience fatal recurrence. Additionally, a substantial fraction of patients treated with trastuzumab, which accounts for 25% of all patients, develop recurrence while for the remaining 75% no targeted therapeutic approach exists [8]. Recent evidence suggests that the main 'problem' is the resistance to therapy. Therefore, there is a crucial need to overcome resistance. The development of more effective therapeutic options and the identification of predictive and prognostic biomarkers to select in an appropriate way those patients who will benefit from specific therapies and who will not present resistance to therapy is now mandatory.

Mechanisms & ways to prevent or treat metastases

All the scientific effort nowadays is accumulating at creating a comprehensive catalogue of all the genes responsible for the initiation, progression and metastatic potential of many types of cancer and this effort represents a major challenge. It is a common topic that patients die because of metastases. The major hope is to prevent or treat in an efficient way metastatic disease [9,10].

Recent studies involve the sequencing of tumor-normal pairs of clinical samples followed by sophisticated mathematical models to analyze and identify those genes in which mutations occur more frequently [9]. Comprehensive knowledge of the genes underlying a 'plethora' of cancers is a critical 'topic' for cancer therapeutics. Identifying which mutations are likely to be drivers and elucidating how these genes affect the metastatic potential of a specific type of tumor can lead the researchers to explore the mechanisms underlying metastatic progression [9–11].

Recent insights have emerged from comprehensive studies using next-generation sequencing (NGS) technologies, which have permitted the sequencing of the coding portion of the genome (all genes) termed as whole-exome sequencing (WES) and the sequencing of the coding as well as the non-coding part of the genome, termed as whole-genome sequencing (WGS) [9,11,12].

Next-generation sequencing technologies

It should be noted that before the use of these NGS technologies, important studies were performed using micro-arrays, PCR amplification and Sanger-based capillary sequencing methods [13]. However, as mentioned above, it is now possible with NGS technologies to use sophisticated genomic analysis to discover specific mutated cancer genes. Recent studies have highlighted a plethora of cancer genes revealing important tumorigenic pathways and potential druggable targets [9,11–13].

In gastric cancer setting, according to the largest catalogue of somatic mutations in cancer (COSMIC) [14], the top genes frequently mutated identified by these techniques up to date include *TP53, APC, CDH1, TRRAP, PIK3CA, MLL3, RNF213, KMT2D, MLL, CTNNB1, CREBBP, AKAP9, CACNA1D, MYH9, ZNF521, SETBP1, KRAS,CDH11, ATM.* These mutations need extensive investigation in order to 'understand' tumorigenesis, cancer progression, tumor resistance and metastases [14]. These genes and mutations represent a preliminary list of gastric cancer driver genes and mutations.

NGS technologies have undoubtedly revolutionized cancer research. Recently, gastric cancer genomics using NGS have reported important findings. The first reported WES study in gastric cancer by Wang *et al.* [15] has analyzed 22 tumor-normal pairs of gastric cancer tissue. They have confirmed previously known drivers genes such as *TP53, PTEN* and *CTNNB1*. One major finding from the study is the high mutation frequency of *ARID1A*, a key member of the SWI-SNF complex. This mutated gene has also been identified in other cancer types (ovarian cancer). Notably, Wang *et al.* [15] also found chromatin modification pathways to be the most 'altered' pathways in gastric cancer. Then, using Sanger sequencing to further evaluate *ARID1A* in additional samples of gastric cancer, they found that the somatic mutation rate of *ARID1A* significantly varies between different types of gastric cancer such as microsatellite instability or infected with Epstein–Barr (EB) virus. Notably, alterations in *ARID1A* are robustly associated with better prognosis independently from the final stage of the tumor.

In addition, *ARID1A* was also discovered as an important driver gene in another WES study in which Zang *et al.* [16] analyzed 15 tumor-normal pairs of gastric cancer. The results of this study highlighted the crucial tumor suppressor role of *ARID1A*. In addition to *ARID1A*, Zang *et al.* [16] discovered also *FAT4*, a member of the E-cadherin family, as an important driver gene for gastric cancer. The researchers showed that *FAT4* gene has a 'key' role as a tumor suppressor in gastric cancer setting [16].

Whole-genome sequencing

Although WGS provides information not only for protein-coding genes, but also for non-coding regulatory genome, bioinformatics big data analyses are still experimental. One of the largest WGS available for any cancer type is the recent study reported by Wang *et al.* [17]. They have included 100 gastric cancer patients with tumor-normal tissue WGS pair analyses, along with DNA copy number, gene expression and methylation profiling. They have found subtype-specific genetic mutational signatures and epigenetic alterations. Interestingly, Wang *et al.* [17] confirmed previously known genes such as *TP53*, *ARID1A* and *CDH1* and discovered novel significantly mutated genes such as *MUC6*, *CTNNA2*, *GLI3* and *RNF43*. Notably, they have also revealed *RHOA* mutations in approximately 15% of diffuse-type tumors but not in intestinal-type gastric tumors. The researchers concluded that these findings illustrate a multidimensional genomic landscape that highlights the high complexity of gastric cancer. They support that maybe we are at the beginning of a genome-guided personalized therapy era of gastric cancer [17].

Recently, another WGS study for gastric cancer was published by Wong *et al.* [18]. The researchers performed WGS analyses of 49 tumor-normal gastric tissues pairs; 31 samples with diffuse and 18 samples with intestinal histological types were included, respectively. Notably, the diffuse-type gastric cancer samples showed significantly smaller numbers of somatic and structural variants compared with intestinal-type gastric cancer. Moreover, they have detected frequent and exclusive mutations in *Ephrins* and *SLIT/ROBO* signaling pathway genes. The authors conclude that this study provides new insights into the mutational diversity-heterogeneity of gastric cancer [18].

Gastric cancer genome heterogeneity & evolution

More recently, the scientific attention has been focused on intratumor heterogeneity and circulating tumor-DNA analyses toward identification of therapeutic resistance and metastases. Novel NGS applications and methods have been developed for assessing intratumor diversity and dynamics of genomic clones evolution [19–23]. Intratumor heterogeneity can be evaluated with multiregional biopsies-based NGS as well as with ongoing single-cell technique for DNA-NGS analyses [20]. Cancer genome evolution can be elucidated with repeated circulating tumor-DNA-NGS analyses [21]. These novel techniques and new methods shape a new horizon in predicting an efficient way for therapeutic resistance in gastric cancer. Moreover, understanding the underlying mechanisms of therapeutic resistance can lead to the development of novel, more effective therapeutic strategies.

In summary, due to recent progress in gastric cancer management and recent use of the cancer genome atlas (TCGA) to find novel targeted therapies [24], therapeutic resistance-based recurrence and disease progression will continue to be a major clinical problem. Looking to the future, it is out of question that genetics, genomics and gastric cancer spatiotemporal evolution will play a crucial role in biomedical research overcoming therapeutic resistance and identifying potential druggable therapeutic targets in the effort to improve or cure patients with gastric cancer.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

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