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Current and future biomarkers in gastric cancer

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ABSTRACT

Gastric cancer is the fourth most common worldwide cause of cancer-related death. Early gastric cancer has no associated symptoms, for this reason, patients come to the attention of the clinicians only in advanced stages. This paper aims to give a global view on the biomarkers for gastric cancer and the therapy in use. We discuss VEGF family, HER family, E-cadherin, PD-L1, and PD-L2, FGFR, mTOR. Finally, we considered emerging biomarkers as MET, microsatellite instability, and microRNA variations. Furthermore, we have analyzed in depth the chemotherapeutic and adjuvant therapies used in the clinic nowadays, comparing the overall and progression-free survival between them. Identifying and validating diagnostic, prognostic, predictive, and pharmacodynamic biomarkers will be mandatory to the huge impact on patients' outcomes and for improving the efficiency of the drug development process.

1. Introduction

In Eastern Asian countries and Western Europe, it is estimated that one million people per year are affected by gastric cancer (GC). The incidence rate in men is double that of women, incidence increases with age and moreover certain ethnic groups have significantly higher risk of disease. GC is the fourth most common malignancy and the second leading cause of cancer-related death worldwide, in most cases (80%) the disease is discovered in advanced stages [1–4]. In the initial stages the symptoms are non-specific. It goes from a vague stomach ache or abdominal pain to vomiting, anorexia, weight loss, difficulty swallowing, excessive belching and sense of early repose (with any meat intolerance). For this reason, very often the disease is diagnosed at advanced stages and this negatively affects patient's outcomes. From the histological point of view there are two main types of stomach cancer. Intestinal stomach cancer is the most common and predominantly affects men over the age of 50. It is associated with the so-called intestinal metaplasia, i.e. the transformation of the gastric epithelium into another type of epithelium, very similar to that of the intestine. These tumors usually appear as formations facing the inside of the cavity and with expansive growth. The other one, is the diffuse type. It is slightly less frequent than the first and affects indifferently men and women of average age over 45 years. In general, the neoplasm arises from the normal gastric mucosa and, penetrating into the tissue, can give rise to ulcers: in this case we talk about a stomach in a leather bag plastic, to underline how growth can lead to hardening of the organ walls. Characteristic of this type of tumor is the presence of cells that under the microscope resemble a ring with an embedded gem ("ring-shaped" cells) [5,6].

Several factors put forward to explain the origin and development of stomach cancer; among them, dietary factors [7], the Helicobacter pylori infection, a family predisposition and more rarely a gastric polyposis.

The diagnosis of stomach cancer is performed by laparoscopy and

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gastroscopy: the same test allows both to observe the inner lining of the stomach and to biopsy. Before being subjected to surgery, it is also necessary to evaluate the possible remote spread of the tumor by computed tomography scan (CT scan) or ultrasound and in some cases echoendoscope may also be useful to evaluate the degree of infiltration of the stomach wall [8].

An accurate preoperative staging of nodal involvement is currently a diagnostic challenge in GC, because of the greatest potential for harbouring metastatic disease; the gold standard method is the multi-detector computer tomography [9,10].

Despite that GC still remains a problem of public health around the globe, the growths in surgical and adjuvant treatment approaches. The utmost surgical resection suggests a potential for curative therapy, ca. 50–70% within 5-year of survival, if a primary diagnosis been formulated. The chances of recovery and the choice of treatment depend on the stage of development of the tumor (from the fact that it is localized only to the stomach or that it is propagated to other areas) and from the general conditions of the patient. When possible, surgery is the treatment of the first choice and the surgery involves the removal of the entire stomach or a part of it; in other cases, the core selection treatment is chemotherapy. However, the average overall survival (OS) less than 1 year of advanced disease remains been associated with best supportive care (3–5 months) [11,12].

This review aims to resume biomarkers useful to monitor and to predict the response to treatments that have been studied in clinical trials and provide up-to-date information on the therapies used nowadays in GC care.

2. Predictive biomarkers in gastric cancer

For instance, clinical parameters like TNM (size of Tumor, lymph Nodes, Metastasis) production, tumor location, gender and histological subtype are incapable to separate responders from non-responders. An additional intricacy in the treatment of gastric cancer is the use of unconventional methods based on the tumor site of origin rather than considering their biological characteristics. The different response to chemotherapy is probably due to the genetic composition of the tumors and the different activated cellular pathways. Advances in molecular biology confirm that a cancerous phenotype is really motley, because it is composed by a plethora of cells that differs each other's by a sum of genetic and epigenetic changes, selected to have a selective survival advantage to clones of cells [13–15].

A cancer predictive biomarker is defined as an objectively measured characteristic (i. e. a circulating protein, particular circulating cells or mutated DNA) which can be used to describe a normal or abnormal physiological state and to identify whether a patient has a specific disease condition (diagnostic), to measure the risk for a subject to developing cancer in a specific tissue and are associated with recurrence, death or other clinical outcome (prognostic) and finally, even to foresee responsiveness to standard chemotherapy or novel molecular targeted therapy and help to determine which patients will benefit with particular types of treatment (predictive) [13,16–19].

An ideal predictive marker should be reliable, readily available and detectable by reasonably acceptable laboratory techniques. It should be highly specific and its levels should be related quantitatively to tumor volume with a very low false-positive rate and a reasonable low false-negative rate [13].

The role of predictive biomarkers has been well established in solid tumours as examples breast cancer [20], chronic myeloid leukaemia [21], lung cancer [22], brain tumours [23] and colorectal cancer [24]. Mining predictive markers in gastric cancer at a genetic, epigenetic, transcriptional and translational level is an area of ongoing research [25]. However, these published works on molecular predictors in gastric cancer are referring to small non-randomized surveying studies and often consist of patients treated with a selection of different treatment regimens. Even though these studies offer valuable insights to understand the importance of molecular biomarkers as prospective randomized control trial assessment parameter however their accurate predictive value standardization is necessary to explore for further [25].

2.1. The genetic biomarkers

2.1.1. Chemotherapeutic drugs and their targets

Cytotoxic chemotherapy agents whose mechanisms of action is based on cell death or prevention of cell growth, usually over inhibit microtubules, cytoskeleton and protein function, nucleic acids synthesis, autophagic DNA damage and topoisomerase destruction, could be cell cycle-dependent are frequently attractive for cell cycle arrest at various stages of cellular growth [25–30]. The efficacy of antitumor therapy is therefore also hindered by the different mechanisms of chemo-resistance expressed in the various cell subclones, single mutations that disable apoptosis can produce drug resistance [31–35]. The best therapeutic strategy is, therefore, to associate multiple drugs together (polychemotherapy) [36–39]. Cytotoxic drugs can act according to two main mechanisms: direct interaction with DNA (i. e. alkylating agents) [27,40] or interaction with the biosynthetic pathway of DNA and RNA precursors (i. e. antimetabolites) [41,42].

Platinating agents (cisplatin and oxaliplatin) [28], 5-FU [43,44], capecitabine [45], anthracycline [46,47] and ionizing radiation [48] are the predominant cytotoxic agents used in the treatment of oesophagogastric cancer [46,49]. The cellular responses involved in mediating the cytotoxicity of these agents are complex (Fig. 1) [25].

Mammalian cells have a highly conserved DNA damage sensor mechanism to ensure a correct progression of the cell cycle them could coordinate the various stages of its reproductive cycle preventing starting of cell division before the DNA is completely terminated or if there are damaged chromosomes, blocking replication protecting to potentially cytotoxic variations. These include induction of apoptosis with the purpose to eliminate heavily damaged cells after the detection of DNA damage and consequent modulation of cell cycle progression to repair damaged or incompletely replicated chromosomes. Aggressive cancerous cells could change their transcriptome as an environmental response or establish a damage-tolerance mechanism to respond to genomic variations [50]. For instance, DNA repair mechanisms that activate cancer cells to repair DNA-damaging lesions made by cytotoxic agents contribute to therapeutic resistance. Instead, sub-optimal DNA restoration of normal tissue might negatively influence on normal tissue tolerance. One of the most pervasive characteristics of human tumors is genomic instability.

Some cytotoxic agent can introduce a single-base nick that could result in single nucleotide polymorphism (SNPs) and therefore a genomic variation.

Most SNPs have no effect on health or development, however, sometimes, this substitution could be a mutation that alters the amino acid sequence of the encoded proteins or alter RNA splicing and in consequence the gene transcription [25,51]. In addition to SNPs, short tandem repeats [52], microRNAs [53], and other genomic variations such as structural variations have been reported to be associated with gastric cancer [54]. Moreover, mutation could alter drug metabolism or drug targets, could activate survival signaling pathways or inactivate downstream death signaling pathways leading to drug resistance [55,56].

2.1.2. Microsatellite instability

Microsatellite markers, or short tandem repeats, are polymorphic DNA loci containing 2–7 repeated nucleotide sequences per unit; the number of repeats for a specific locus may differ, resulting in alleles of varying length. During the replication of this repetitive DNA, due to the slippage of DNA-polymerase may arise base-pairing mistakes that are normally repaired by the mismatch repair system. Defects in the repair of misalignments lead to an accumulation of mutations. Recently, has proved that assessing the microsatellite instability is an efficient tool for