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Tumour Review

Unmet needs and challenges in gastric cancer: The way forward

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ABSTRACT

Although the incidence of gastric cancer has fallen steadily in developed countries over the past 50 years, outcomes in Western countries remain poor, primarily due to the advanced stage of the disease at presentation. While earlier diagnosis would help to improve outcomes for patients with gastric cancer, better understanding of the biology of the disease is also needed, along with advances in therapy. Indeed, progress in the treatment of gastric cancer has been limited, mainly because of its genetic complexity and heterogeneity. As a result, there is an urgent need to apply precision medicine to the management of the disease in order to ensure that individuals receive the most appropriate treatment. This article suggests a number of strategies that may help to accelerate progress in treating patients with gastric cancer. Incorporation of some of these approaches could help to improve the quality of life and survival for patients diagnosed with the disease. Standardisation of care across Europe through expansion of the European Registration of Cancer Care (EURECCA) registry – a European cancer audit that aims to improve quality and decrease variation in care across the region – may also be expected to lead to improved outcomes for those suffering from this common malignancy.

Introduction

Gastric cancer (GC) is the fourth most common cancer worldwide, with 980,000 cases being diagnosed in 2008, 83,000 of which were in the European Union [1]. While dietary improvements and reduction in chronic *Helicobacter pylori* infection due to the use of antibiotics have resulted in a steady fall in incidence and mortality rates in developed countries over the past 50 years [2], outcomes in Western countries remain poor. In Europe, overall 5-year survival from GC is around 25%, contrasting with a 70% survival rate in Japan [3,4]. These differences reflect the fact that the disease is often diagnosed at an early stage in Japan due to screening, while in the West the disease is frequently at an advanced stage at presentation [2]. While earlier diagnosis would help to improve outcomes for patients with GC, a better understanding of the biology of the disease is also needed, along with advances in therapy.

Pathogenesis of GC

Most GCs are gastric adenocarcinomas, which are malignant epithelial neoplasms. However, GC is a highly heterogeneous entity with respect to patterns of architecture and growth, cell differentiation, histogenesis and molecular pathogenesis. Currently, five

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major types are recognised by the World Health Organization (WHO) classification: papillary, tubular and mucinous adenocarcinoma, poorly cohesive carcinoma (with or without signet ring cells) and mixed carcinoma [5]. Two major types of GC were described by Laurén – intestinal and diffuse [6]. These display different clinicopathological profiles and molecular pathogenesis, and often occur in distinct epidemiological settings [7]. Intestinal type carcinomas generally occur in older patients and are thought to arise through a background of chronic gastritis with progression to intestinal metaplasia, dysplasia and gastric carcinoma [7,8]. Progression of chronic atrophic gastritis has been shown to be associated with *H. pylori* infection, with risk of developing GC being dependent on strain virulence and host susceptibility [9–12]. The diffuse type is more common in younger individuals and its pathogenesis is less well understood [13]. Tubular and papillary carcinomas (WHO classification) roughly correspond to the intestinal type described by Laurén, and poorly cohesive carcinomas (encompassing cases constituted partially or totally by signet ring cells) correspond to the diffuse type. Rare variants account for about 10% of gastric carcinomas and a further 10% are thought to be caused by Epstein–Barr virus [14].

Most GCs (90%) are sporadic. Familial clustering is observed in 10% of cases and only 1–3% of GCs are hereditary, comprising hereditary diffuse gastric cancer (HDGC) [15–17] and the recently described gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) [18]. The molecular pathogenesis of GC is complex. One of the key molecular features in sporadic cancers is the amplification of human epidermal growth factor receptor 2 (*HER2*). Around 15% of patients have HER2-positive (HER2+) GC in clinical practice, though the proportion is higher in those with intestinal GC (33%) and lower for individuals with diffuse disease (6%) [19]. HER2 may also have a prognostic role in GC, though the association remains controversial [20]. Epidermal growth factor receptor (EGFR) is also over-expressed in around 40% of GCs [21]; however, its role in the pathogenesis of the disease is unclear. Most HDGCs are caused by alterations of the E-cadherin gene (*CDH1*) [22–24], with a minority thought to be due to α-E-catenin [25]. E-cadherin mutations may also influence the sporadic form of the disease and may present a target for novel cancer therapies. The gene responsible for the recently described GAPPS syndrome has not been identified to date [18].

The timescale of the progression of normal gastric mucosa to gastric carcinoma is 10–20 years, yet most cases present at an advanced stage due to the asymptomatic nature of early-stage disease, emphasising the need for earlier diagnosis to improve the possibility of cure. However, current Western guidelines recommend gastroscopy only for symptomatic patients or those with a family history of GC, with prophylactic gastrectomy being recommended for individuals with a genetic predisposition for HDGC [23,26,27]. National screening for *H. pylori* to reduce GC risk has the potential to reduce mortality, but is only likely to be cost-effective in countries with the highest incidence of the disease (e.g. Japan).

Genomic approaches to GC heterogeneity

A range of therapies are available for the treatment of GC, though the molecular and clinical heterogeneity associated with the disease creates an urgent need to apply precision medicine to management to ensure that individuals receive the most appropriate drugs. In recent years, efforts have concentrated on translational research in order to identify key alterations in GC that may represent important targets for novel therapies. These studies have revealed a number of commonly mutated genes, of which tumour protein 53 (*TP53*) is the most frequently found, though active mutations can also be identified in phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) (which governs mammalian target of rapamycin [mTOR] signalling) and *CTNNB1* (Wnt signalling) [28]. Mutations in chromatin remodelling genes (*ARID1A, MLL3* and *MLL*) are also common, occurring in more than 40% of GCs. In particular, *ARID1A* mutations have been found in up to 10% of tumours, often concurrent with microsatellite instability and *PIK3CA*-activating mutations. *ARID1A* may also be a novel tumour suppressor gene, presenting possible therapeutic opportunities [28]. Receptor tyrosine kinase (RTK)/*RAS* amplifications (e.g. fibroblast growth factor receptor 2 [*FGFR2*], *ERBB2/HER2*, *EGFR* and *MET*) are further frequent alterations in GC, and around 37% of patients may be potentially treatable with RTK/RAS-directed therapies (Fig. 1) [29]. Additionally, DNA methylation alterations are present in around 40% of GC tumours [30], suggesting a role for epigenetic agents in the treatment of the disease. Activating mutations in *KRAS* are rare in GC, though gene amplification of wild-type *KRAS* is frequent and confers a poor prognosis [29].

Recently, gene expression profiling using mRNA consensus clustering has revealed three distinct GC subtypes – mesenchymal, proliferative and metabolic (Table 1) [31]. It is hoped that the distinct molecular and genetic features displayed by these newly-identified subtypes and the differences in their responses to treatment may help in the quest to develop more personalised therapy for patients with GC. For example, the results of preclinical studies suggest that mesenchymal-subtype GCs may be more sensitive to PIK3CA/mTOR/AKT pathway targeting drugs compared with GCs of other subtypes.

Current treatment of localised GC

Surgery is the only means of cure for patients with GC and is the treatment of choice for early-stage disease. Endoscopic resection may be used as an alternative to surgery for early-stage tumours if they are well differentiated (⩽2 cm), confined to the mucosa and not ulcerated (Fig. 2) [32]. The primary goal of surgery for localised GC is a complete resection with negative margins (R0) [33–36]. The value of surgical expertise in GC is highlighted by the considerable variations in GC cure rates reported in different regions. In particular, surgery for patients with locally advanced GC is curative in around 80% of patients in Japan, though the percentage is much lower in the West (up to 55%). Indeed, experience from Japan has underlined the efficacy of more extensive lymph node dissection (D2 rather than D1) coupled with longer-term

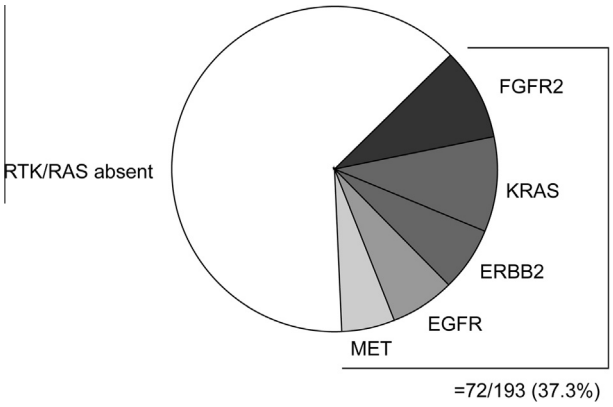

Fig. 1. Frequency of receptor tyrosine kinase (RTK)/RAS genomic alterations in gastric cancer. Reproduced from Deng et al. [29]. Different gastric cancer subgroups exhibiting RTK/RAS amplification. Gastric cancers exhibiting at least one RTK/RAS amplification event comprise a collective 37% of the cohort analysed. EGFR, epidermal growth factor receptor; FGFR2, fibroblast growth factor receptor 2.