

Gastrointestinal Stromal Tumors Short Review on KIT/PDGFR Gene Mutations and Molecular Therapy

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Abstract

Gastrointestinal stromal tumors (GISTs) are most frequent mesenchymal neoplasms of the gastrointestinal tract. Current knowledge demonstrates that the KIT and PDGFR gene mutations play a central part in the pathogenesis. Mutations can be subdivided into primary and secondary mutations. Secondary mutations usually occur in KIT kinase domains after tyrosine kinase inhibitors treatment resulting in resistance to drugs. Besides surgery, therapy with tyrosine kinase inhibitors has led to develop novel treatments for patients now. However, secondary resistance has become a significant concern, illustrating the need to increase collaboration between surgical management and molecular therapy.

Keywords: Gastrointestinal stromal tumors; KIT and PDGFR mutations; Target molecular therapy

Introduction

Gastrointestinal stromal tumors (GISTs) are most frequent mesenchymal neoplasms of the gastrointestinal tract and mostly arise from the muscularis propria [1]. The key molecular step in carcinogenesis is those sporadic mutations within the interstitial cells of Cajal (ICC) [2]. Activation of KIT or platelet-derived growth factor receptor alpha (PDGFR) gene mutation is a major force in GISTs. As reported, 95% of GISTs express KIT, and more than 80% have gain of function mutations of KIT or PDGFR [3]. Abdominal pain and gastrointestinal bleeding were the more common symptoms [4]. This review will elucidate KIT and PDGFR mutations and target molecular therapy of GISTs.

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors demonstrated predominantly gastric location, followed by the duodenum and small intestine. It was widely believed reported that GISTs were mostly located in the stomach [5,6] followed by small intestine. It was reported in southern Thailand that about 30% already had metastasis at presentation and the most common metastatic location was the liver [6]. If GIST ruptures into the abdominal cavity, patients have a high risk of recurrence [7]. Abdominal pain and gastrointestinal bleeding were the predominant presenting symptoms. From a retrospective observational study in Afro-Caribbean patients, we can see that and gastrointestinal bleeding (50%) and abdominal pain (44%) were the most common presenting symptoms. Male to female ratio was 1.25:1, the mean age was 54.7 years [8]. The symptomatic GISTs of the esophagus was typically dysphagia [9]. The diagnosis of GISTs is currently based on morphologic features and typically characterized by the expression of KIT/PDGFR [10]. Combined detection of CD117 and CD34 benefits the diagnosis of GISTs [11]. Generally speaking, GISTs are detected during a gastroscopy as submucosal nodules or incidentally radiographs. While the positive rate of gastroendoscopic biopsy was low [12]. As reported, some esophageal GISTs analyzed were seen as esophageal masses in routine chest X-ray [13,14]. Small GISTs are often detected as incident on gastric or small intestinal serosa during surgery for other conditions, such as, during gall bladder surgery [15]. The definition specifically excludes gastrointestinal true smooth muscle tumors, such as leiomyomas and schwannomas, which were negative for CD117, CD34, or showed focal positivity for PDGFR-alpha (1/9), with no mutations found [16].

The KIT and PDGFR Mutations

The mutations of the KIT and PDGFR gene play an important role in the pathogenesis of GIST. And a large number of data indicate that genetic characteristics are critical risk factors for recurrence. Recent studies have shown that the ligand for the c-kit receptor not only is stem-cell factor, but also steel factor. Mutations of KIT cause constitutive activation of the tyrosine kinase function of KIT [17]. Mutations can be subdivided into primary and secondary mutations. The most common primary mutations are being observed in exon 11 in the 3 region of KIT exon 11, occurring in 62% of cases. In addition, KIT mutations often involve exons 9, 13 and 17 [18]. A rare mutation, an Ala502-Tyr503 duplication in exon 9, is specific for intestinal GISTs [19]. The KIT genotypes after imatinib mesylate resistance may both relate to primary mutations, KIT exon 11 mutations were detected, which were all acquired mutations, including exon 13 V654A, exon 13 V654E and exon 17 N822K [20]. Mutations of the KIT kinase domains are very rare, substantial data show that PDGFR-alpha mutations are found in up to 20% in GISTs [21]. A few GISTs have been found to have mutations only in the PDGFR gene. It is reported that PDGFR gene mutations are nearly specific for gastric GISTs, especially those with epithelioid morphology [22]. These PDGFR mutations involve exons 14, 12 and 18. The majority of PDGFR mutant GISTs have weak or negative CD117 expression [23,24]. Within the KIT and PDGFR gene, the mutations resulted in constitutive tyrosine kinase activity, leading to downstream phosphorylation of substrate proteins and subsequently activation of networks of signal-transduction pathway. The secondary mutations are developing during the treatment with tyrosine kinase inhibitors and leading to secondary drug resistance [25]. However, about 15% of GISTs are wild-type (WT) GISTs and do not show either KIT or PDGFR mutations. Patients with WT GIST are typically less sensitive to tyrosine kinase inhibitors [26,27]. This group includes sporadic WT GIST, paediatric GIST and neurofibromatosis type-1 (NF1)-related GIST [28-40].

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