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Review

Sunitinib in the management of gastrointestinal stromal tumours (GISTs)

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Abstract

Aims: Gastrointestinal stromal tumours (GISTs) are rare mesenchymal neoplasms of the gut with a 5-year survival of ~50%. Surgery remains the treatment of choice in resectable disease, with conventional chemotherapy largely ineffective. Over 90% of GIST possesses mutations in the *c-KIT* oncogene, producing an overactive tyrosine kinase, which may be driving the malignant process. Imatinib inhibits the aberrant tyrosine kinase and imatinib therapy in metastatic disease has shown significant clinical benefit. However, resistance typically develops within 2 years, with the need for further therapy. This article aims to introduce the reader to a new development in cancer therapeutics.

Methods: A literature search was performed using the MEDLINE database to identify publications relevant to the review. References within these articles were used to expand the search. Abstracts from recent ASCO symposia were hand searched for relevant articles.

Findings: Sunitinib (SU11248) is a novel multi-targeted tyrosine kinase inhibitor with activity not only against the receptor tyrosine kinase product of c-KIT but also other cell-signalling pathways that may be relevant in GIST; FLT3, platelet-derived growth receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR). Two Phase II trials and one Phase III trial have investigated the activity of sunitinib against imatinib-resistant GIST. Early results showed significant benefits in time to disease progression that led to licensing of the drug in America and more recently in Europe. A Phase III trial comparing dose-increased imatinib and sunitinib in progressed GIST is currently planned.

Conclusions: Initial clinical results with sunitinib are promising and suggest a future role. Further studies are needed before sunitinib can be recommended for the routine treatment of imatinib-refractory GIST.

Keywords: Gastrointestinal stromal tumour; GIST; Sunitinib; Phase III trial; Protein kinase inhibitors

Introduction

Cytotoxic chemotherapy agents act by disrupting DNA synthesis and cell division. These agents are effective in many cancers, but may be toxic because of low selectivity. Tumour resistance is also common.[1] Increased understanding of cancer at the level of cell signalling, rather than histology, has led to the identification of targets specific to individual tumours. This has the potential of less drug resistance and lower toxicity.

Tyrosine kinases (TKs) are key components of many cell-signalling pathways involved in neoplastic transformation. Over 90 TKs have been described to date: transmembrane receptor tyrosine kinases (RTKs) transduce extracellular signals triggered by ligand binding, whereas cytoplasmic TKs relay intracellular signals (Fig. 1). Genes encoding TKs constitute the largest class of oncogenes, and inappropriate TK signalling is a key feature of malignant transformation.[2,3] Aberrant signalling can occur through several mechanisms, including ligand overexpression, deregulating

Abbreviations: FDA, Food and Drug Administration; FLT3, fms-like tyrosine kinase-3 receptor; GIST, gastrointestinal stromal tumour; MTTP, median time to progression; PDGFR, platelet-derived growth factor receptor; RTK, receptor tyrosine kinase; TK, tyrosine kinase; VEGFRs, vascular endothelial growth factor receptors.

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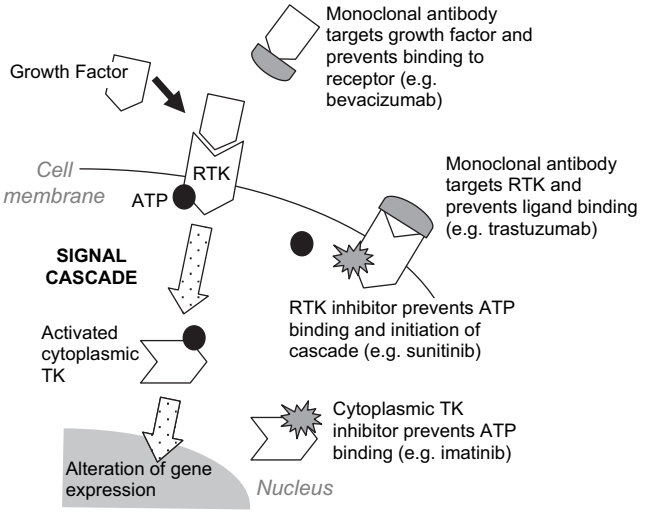

TK - tyrosine kinase, RTK - receptor tyrosine kinase, ATP - adenosine triphosphate.

Figure 1. Diagram summarising signal transduction and sites of action of anticancer agents.

mutations within the RTK itself, and RTK overexpression resulting from amplifications or translocations.[4]

Early work using recombinant techniques showed that inactivation of key TKs is sufficient to reverse-transform cells, suggesting a central role in malignant transformation.[5] As TKs are therefore promising therapeutic targets, several strategies have been used to disrupt pathways where they are overactive. Monoclonal antibodies are one such method, with agents such as bevacizumab showing significant potential.[6,7] Small molecule therapies, including imatinib,[1] represent an alternative approach. Some of these new agents may provide treatment options for previously chemoresistant cancers such as gastrointestinal stromal tumours (GISTs).[8] The use of the small molecule tyrosine kinase inhibitor sunitinib malate (Sutent®; SU11248; Pfizer) in the treatment of GIST forms the focus of this review.

Gastrointestinal stromal tumours (GISTs)

Gastrointestinal stromal tumours (GISTs) are mesenchymal neoplasms thought to arise from interstitial cells of Cajal.[8] They account for 1–3% of all gastrointestinal malignancies, with an incidence of 6–20 per million population.[9,10] Patients generally present aged 50–80 years, usually with painful abdominal masses, gastrointestinal bleeding or bowel obstruction.[10] Most tumours arise in the stomach, with the small intestine the next most common site.[11] The liver is the primary site of metastasis.[8]

GIST and the KIT oncogene

GISTs appear to carry a characteristic genetic abnormality in the *KIT* oncogene; cell signalling through KIT is almost invariably abnormal in this tumour, and may be central to its pathogenesis.[12] KIT signalling has been implicated in cell proliferation, differentiation and survival[13] and its expression is required for the normal development of the GIST precursor cell-type.[12] Histological similarities meant GIST was previously widely classified as a leiomyosarcoma, but diagnosis is now made by immunohistochemistry, staining for KIT.[8,12] The ligand of KIT, stem cell factor, induces dimerisation of receptors and activates an RTK-signalling pathway.[10] Activating KIT mutations are an early step in tumourigenesis, with such mutations found in 85–92% of tumours at various points: exon 11 in 67% of tumours (altering an intracellular regulatory domain); exon 9 in 18% (altering an extramembrane domain); and exons 13 and 17. A small proportion of tumours have no apparent KIT mutations ('wild-type').[8,10,14]

It has been proposed that gain-of-function KIT mutations provide a growth promoting and anti-apoptotic signal to malignant cells.[13] However, KIT is not the exclusive abnormality in GIST; activating PDGFRα platelet-derived growth factor receptor-α (PDGFRα) mutations are found in 5% of tumours and have also been implicated in the pathogenesis of GIST.[10,14]

Current management of GIST

Surgical resection is the first-line treatment of GIST, with a 5-year survival of 48–54%.[15,16] For tumour diameters >10 cm, this figure drops to 20%.[8] Recurrence rates vary, with features such as tumour stage and mitotic rate being important prognostic markers at presentation,[17] but one study found 40% of tumours recurred over a 24-month period post-surgery.[18] Response rates to conventional chemotherapy agents are extremely low[13] and prognosis for recurrent GIST is very poor with a median survival of 15 months post-resection.[12,19]

The introduction of the TK inhibitor imatinib mesylate (Glivec®; Novartis) transformed the management of metastatic GIST. Although originally developed to inhibit the kinase product of the *bcr-abl* fusion gene, found in 95% of chronic myeloid leukaemia patients,[20,21] imatinib was also found to inhibit GIST cell lines.[22] Clinical trials showed dramatic efficacy: 76–88% of patients with recurrent GIST showed a response to treatment,[8] with a median duration of response of up to 2 years. The median survival of patients with metastatic disease increased from 1 to 5 years with imatinib therapy.[23] In 2004, the National Institute for Clinical Excellence approved imatinib for first-line treatment of unresectable or metastatic GIST.[24] KIT mutation status appears to have a significant impact on treatment response. Patients with the commonest exon 11 mutation experience higher rates of tumour shrinkage and prolonged survival, when compared to patients with exon 9 mutations, other mutations, and apparently wild-type GIST.[25]

Despite its initial success, the majority of patients eventually cease to respond to treatment, defined as either