Imatinib-refractory Gastrointestinal Stromal Tumors: The Clinical Problem and Therapeutic Strategies

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Introduction

Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors of the intestinal tract. Before their identification as a distinct biologic subtype, they were termed leiomyosarcomas, leiomyomas, or leiomyoblastomas. They were renamed GISTs with the recognition that they contained smooth muscle and neural features [1•]. Subsequently, these tumors were found to express CD34 and KIT [2,3]. Most tumors contain mutations of KIT resulting in constitutive activation of the molecule and serving as the biologic driver of these tumors [4•]. Standard therapeutic approaches other than surgery were shown to be ineffective in patients with GIST. Imatinib mesylate (imatinib) is an oral agent that competitively inhibits binding of ATP to various tyrosine kinase molecules including ABL, BCR-ABL, KIT, platelet-derived growth factor receptor (PDGFR), and TEL. After its tremendous success in chronic myelogenous leukemia targeting BCR-ABL, imatinib was tested in GIST in patients with tumors that expressed KIT.

The incidence of GIST is being clarified as pathologists, surgeons, and medical oncologists identify the disease correctly. A population-based study from Iceland of GIST diagnosed between 1990 and 2003 estimated the annual incidence to be 1.1 per 100,000 population [5]. A population-based study of western Sweden identified 288 primary GISTs between 1983 and 2000, with an annual incidence of 14.5 per million and estimated overall prevalence of 129 per million [6]. The Surveillance, Epidemiology, and End Results Registry (SEER) database identified cases diagnosed between 1992 and 2000 and determined the age-adjusted yearly incidence rate was 0.68 per 100,000 [7]. The median age at diagnosis in these cohorts was 65.8 and 63 years, with some studies suggesting an increased incidence among men. The SEER database analysis also suggested a higher incidence in blacks. Prognostic factors associated with a poor outcome were older age, black race, advanced stage, and lack of therapy.

The most common site of primary tumors is the stomach (39% to 70%), followed by the small intestine (31% to 45%), colon, rectum, and anus (10% to 16%), and mesentery and peritoneum (8%), with rare cases arising in the esophagus [8,9,10•,11,12]. Case reports in the literature also describe primary tumors of the duodenal ampulla [13], appendix [14], gallbladder, and urinary bladder [15]. Metastatic disease is most commonly found in the liver and the peritoneum and omentum. Less common sites of disease include lung and bone.

Treatment

Treatment for gastrointestinal stromal tumors until the 21st century was primarily surgical. Complete en-bloc surgical resection of the primary...
tumor is the goal of surgery for primary tumors, without need for a lymph node dissection. The data regarding the efficacy of surgery are retrospective in nature [9,10•,16,17]. These studies indicate that complete resections in all stages of disease, that is, primary presentation, locally recurrent disease, and metastatic disease, lead to prolonged survival compared with patients who have residual disease after resection. They also suggest that up to 50% of patients presenting with primary disease will eventually recur.

Patients with metastatic disease fared poorly in the past. Doxorubicin- and ifosfamide-containing regimens have reported response rates of 0% to 27%, in paclitaxel of 7%, and in gemcitabine of 0% in GIST [18]. A trial of dacarbazine, mitomycin, doxorubicin, and cisplatin revealed a 54% response rate in leiomyosarcomas, compared with a 4.9% response rate in GIST [19]. Other palliative approaches have included chemoembolization [20,21] and radiation, with limited data on their efficacy. The limited response rates with these therapies were associated with poor survival in patients with metastatic disease.

**Molecularly targeted treatment of gastrointestinal stromal tumors: imatinib mesylate**

The outcome for patients with GIST changed significantly with the understanding of KIT as the oncogenic driver of this tumor. Imatinib mesylate (imatinib), a tyrosine kinase inhibitor with activity against ABL, BCR-ABL, KIT, PDGFRα, and cisplatin showed preclinical activity against wild-type and mutated forms of KIT [22••,23••]. A trial of imatinib in one patient with metastatic and heavily pretreated GIST demonstrated significant activity [24•]. Subsequent phase I to III trials have demonstrated safety and significant activity for patients with metastatic GIST. The maximum tolerated dosage was 800 mg daily, with higher dosages associated with excess nausea, vomiting, and fatigue [25]. Phase II data demonstrated activity of the agent at 400 mg, 600 mg, and 800 mg daily [26,27]. Patients had rapid clinical responses and positron emission tomography (PET) scan responses, with conventional radiographic responses taking up to 12 months to occur. The response rates in phase I and II trials of imatinib in patients with GIST were 54% to 71% partial response (PR), with an additional 17% to 37% with stable disease (SD); only 1% of patients achieved a complete response (CR). The phase III trials confirmed the activity of imatinib, although the overall PR rates were lower: CR = 3% to 6%, PR = 45% to 48%, and SD = 26% to 32%, for a total clinical benefit of 76% [28••,29]. The clinical benefits were prolonged, with a median time to progression of 18 to 24 months.

Although some patients had excellent clinical and radiographic responses, two groups of patients that lacked response emerged in these studies. The first were 9% to 17% of patients whose disease never had any stabilization or response to imatinib [26,28••,30,31]. The second group of patients achieved disease stabilization or response on imatinib, but then went on to progress. Clinically this second group contrasts with the first group in that progression is more typically focal rather than involving all sites of known disease.

**Etiology of resistance**

To aid patients with imatinib-refractory disease, we need to understand the underlying biology of the lack of efficacy seen. It is clear that tumors with different types of mutations in KIT and PDGFR have varied response rates to imatinib, as is discussed in the study by Tarn and Godwin [32]. Other possible mechanisms include increased drug efflux or other pharmacokinetic factors, which may be overcome by increasing the dose of imatinib. Molecular changes at the target may also explain the lack of efficacy, such as KIT amplification/KIT deletion, or additional KIT or PDGFRα mutations. Alternatively, KIT inhibition may still be present with a second genetic mutation or activating pathway as a cause of drug resistance. For patients with such alterations in KIT/PDGFR, identifying novel targets for therapy may be of value.