Executive Summary

Gastrointestinal stromal tumors (GIST) are the most common primary mesenchymal tumors of the gastrointestinal tract (80%) [1], representing 5% of all sarcomas [2], with estimated incidence 14.5 per million and prevalence 129 per million [3], and 5000 to 6000 new cases per year in the United States[4]. Median age of diagnosis is 60 with no gender predominance. There are rare cases of pediatric disease, and rare familial cases reported, but the vast majority of cases are sporadic and no risk factors are known. There is limited data for world-wide incidence of disease, but available data indicates incidence of 10-20 per million (mostly based on European populations).

In the last 15 years, tremendous progress has been made in understanding and treating the underlying pathophysiology of GIST; there is very high expression of activating c-KIT or PDGFR-alpha mutations (~85%), and targeted treatment with small molecule tyrosine kinase inhibitors (TKI) has revolutionized the prognosis for GIST. Effective use of these targeted agents is dependent upon being able to demonstrate the specific mutation in a patient’s cancer cells.

Metastatic GIST represents 15-47% of diagnosed disease. Before the use of TKIs for treatment, metastatic GIST was characterized by poor response to cytotoxic chemotherapy and poor prognosis; a median overall survival on chemotherapy of 17 months [5]. With imatinib as first-line therapy, there have been significant improvements in both progression free survival (median PFS ~2years) and overall survival (median OS 57 months) [6]. Sunitinib has shown efficacy as second-line treatment in imatinib refractory or intolerant disease, with median PFS 27-34 weeks vs. 6 weeks in placebo [7][8][9]. In disease that has progressed on imatinib and sunitinib, regorafenib as third-line therapy has demonstrated activity with improved median PFS compared to placebo: 4.8 months compared to 0.9 months in the placebo group [10]. The present proposal recommends the inclusion of imatinib. Sunitinib adds benefit to progression-free survival however given the reported poor quality of life associated with the drug and unclear benefits to overall survival, the committee has excluded this drug from the current proposal. Regorafinib, as a third line drug, was excluded on the criteria that third line therapies were not considered for the present recommendations.

Treatment of localized GIST consists of primary resection, followed by adjuvant treatment with imatinib for patients with high-risk disease. Roughly 60% of patients are cured with surgery alone and are not candidates for adjuvant therapy [11]. Risk stratification is determined by tumor size, mitotic count, and tumor site. Tumor sizes greater than 10 cm are associated with increased risk of recurrence and metastasis despite clean surgical margins. Additionally, tumor rupture, multi-organ involvement also can necessitate use of adjuvant therapy. Adjuvant therapy
GASTROINTESTINAL STROMAL TUMOR
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

reduces rates of recurrence by ~65% , and an increased 5 year overall survival from 82% to 92% [12][13].

Given the tremendous improvements in overall survival and well-tolerated side effects of TKI treatment, we recommend adding imatinib to the Essential Medicines List.

Public Health Relevance

Epidemiological data regarding the global incidence and prevalence of gastrointestinal stromal tumors is limited due to factors such as inconsistencies in nomenclature and in diagnosis criteria [15]. However, one study estimated the incidence in United States to be 1,458 cases between 1992 and 2000 with an overall ASR of 0.68 per 100,000 person-years [16]. The same study determined that incidence rates of GIST increased with increasing age. Another study estimated the annual incidence of clinically detected GIST in Western Sweden in 2005 to be 14.5 cases per million and the prevalence to be 129 per million inhabitants [17]. This study indicated that both global and national incidence rates of GIST have been significantly underreported and that GIST may affect greater numbers of populations than previously thought. In addition, with effective

Requirements for diagnosis, treatment, and monitoring

Diagnostics:
Pathologic laboratory analysis of surgically excised tissue or core needle biopsies is necessary for diagnosis, including immunohistochemistry (KIT[CD117] and/or DOG1), which is present in ~95% of cases. Additional CD117-negative cases can be diagnosed with mutational analysis for mutations involving KIT and PDGFRA genes, although these are rare cases, and the critical aspects of diagnosis remain pathologic review of lesional tissue, together with immunohistochemistry for KIT and/or DOG 1.

Mutational analysis also has prognostic and predictive value for response to targeted therapy. Specifically, c-KIT mutation with Exon 9 involvement (the 2nd most common) has shown poor response to the standard dosing of imatinib and improved response to a higher dose. However, routine mutational testing may not be available world-wide and an acceptable practice would be treat all patients with unresectable and/or metastatic GIST with standard dose imatinib 400mg per day, and only consider dose escalation in cases of poor response.

Testing:
Radiologic imaging is important to distinguish resectable disease from non-resectable and metastatic disease. CT of the abdomen and pelvis is acceptable for this purpose.

Administration and Care of Patients:
Imatinib is an orally administered drugs.

Metastatic disease:
Routine follow-up with labs, exam, and monitoring of side effects of treatment are necessary for dose adjustments and interruptions. The frequency of these can be moderated over time from quite frequently initially (weekly) to 3-6 months eventually. Restaging scans to detect disease recurrence or progression should be done every 3-6 months or more frequently as needed given development of symptoms. If CT imaging is not available, abdominal ultrasound may be considered.

**Adjuvant therapy:**
Routine follow-up with labs, exam, and monitoring of side effects of treatment are necessary throughout the 3 years of treatment. The frequency of these visits can be moderated over time. Restaging scans should be done every 3-6 months for the first 3 years, every 3 months for the following 2 years (off of adjuvant therapy), then every 6 months for 3 years, than yearly thereafter [14], given the vast majority of recurrences within the first 5 years and within the first few years after discontinuing adjuvant therapy.

**Overview of Regimens**

The following tables include basic information on administration and dosing for imatinib and exclude ancillary medications pertaining to the management of side effects. For the therapeutic regimens considered continued therapy is recommended until there is evidence of disease progression or the therapy is no longer tolerated in metastatic disease; at least 3 years of treatment in the adjuvant setting.

**Standard First-Line Regimen for Adjuvant Therapy**

| **Imatinib:** minimum 3 years treatment for patients with resected high risk GIST |
| **Imatinib** | oral | 400 mg daily |

**Standard First-line Regimen for Treatment of Metastatic Disease**

| **Imatinib:** ongoing until progression or intolerance |
| **Imatinib** | oral | 400 mg daily (consider imatinib 400mg BID (total 800mg daily)) |

**Review of Benefits and Harms**

**Benefits**
Imatinib: Improvement in overall survival in the metastatic setting from approximately 1 year to a median OS of 4-5 years[5][6]. In the adjuvant setting, there is an estimated disease progression rate reduction of 65%, and an improvement in 5 year overall survival from 82% to 92% in patients with high risk disease [12]. Neoadjuvant administration can result in unresectable or borderline resectable disease becoming resectable.
Sunitinib: 5-6 month improvement in progression free survival vs placebo in patients who have progressed on imatinib. [7][8][9] Please refer to “Executive Summary” for reasoning on exclusion of sunitinib.

Harms and Toxicity Considerations

Common
Imatinib is generally well-tolerated. Patients may experience mild adverse effects including diarrhea, edema, fatigue or muscle cramps. Higher doses are associated with more side effects. [6]

Sunitinib commonly causes fatigue, hypertension, hand-foot skin reaction, diarrhea, skin-discoloration, and nausea [7][9]. Most reactions are mild-moderate and manageable with dose reduction or interruption.

Patients taking regorafenib experience adverse events more frequently, including hand-foot skin reaction, hypertension, diarrhea, fatigue, and oral mucositis. Events requiring dose interruptions and reductions were seen in 50-60% of patients, however rates of discontinuation were low (< 5%) indicating they are highly manageable with dose adjustment [10]. Patients on regorafenib should be evaluated at least every 2 weeks for the first 1-2 months to ensure tolerance.

Systematic Reviews


Abstract: Constitutively activating mutations in the KIT and platelet-derived growth factor receptor α (PDGFRA) RTKs play a crucial role in the biology of gastrointestinal stromal tumors (GISTs), and this disease has served as an effective model for targeting gain-of-function kinase mutations in cancer. Imatinib has entered the clinical arena in the last decade and substantially improved the outcome in these formerly untreatable cancers. However, most advanced GISTs responding to imatinib progress within 2–3 years due to heterogeneous subclones harboring a range of imatinib-resistant secondary KIT mutations. Sunitinib, and more recently, regorafenib, have obtained US Food and Drug Administration approval for the treatment of GISTs after imatinib failure, and thus expanded the treatment options in resistant disease. Within this framework, we present an evaluation of current GIST management, emphasizing the most recent advances in the field together with a discussion on future steps to be taken in refractory disease.


Abstract: Gastrointestinal stromal tumor (GIST) is a disease that was poorly understood historically. In the last decade, it has undergone a major transformation, sparked by the landmark discovery of the central role of activating KIT mutations in its pathogenesis and recognition of KIT protein expression (CD 117) as a reliable diagnostic marker of disease. The introduction and subsequent US Food and Drug administration approval of
GASTROINTESTINAL STROMAL TUMOR
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

Imatinib mesylate in the treatment of metastatic or unresectable GIST in February 1, 2002 has thrust this hitherto little known disease into the center stage of oncology, and GIST has served as a model for rationally designed drug trials in the field of cancer therapeutics since.


**Summary:** Over a decade has elapsed since the routine use of TKI therapies for the management of advanced GIST. This has led to increased survival for many patients in a disease that was universally lethal within 1 year if disease was unresectable. Today, there are three approved agents for the treatment of GIST, and several other agents in which data support its use. Tumors that are refractory to TKIs remain a challenge and novel combination therapies being tested in the phase I setting will likely lead to new therapeutic options; in particular agents targeting downstream pathways, which have been shown to remain active despite KIT-PDGFRA targeting, such as AKT, are of great interest. In addition, clinicians have come to appreciate that GIST represents a family of tumors with similar histologic features but different molecular drivers. As agents targeting specific mutations or mechanisms are developed it will become increasingly important to genotype patients so as to prescribe appropriate therapies.


**Abstract:** Adjuvant imatinib prolongs recurrence-free survival and probably overall survival of patients who have undergone surgery for gastrointestinal stromal tumor (GIST). Estimation of the risk of recurrence with a prognostication tool and tumor mutation analysis is essential before imatinib initiation, because approximately 60% of patients with GIST with operable tumor are cured by surgery alone and some mutated tyrosine kinases are insensitive to imatinib. Adjuvant imatinib is usually administered for 3 years at the dose of 400 mg once daily. Early detection of tumors that recur despite adjuvant therapy with longitudinal imaging of the abdomen is likely beneficial.

**Recommendations**

The reviewers recommend the incorporation of GIST cancer treatment options into the WHO Model List of Essential Medicines, and recommend specifically that imatinib be added to the core Essential Medicines List.

**Additions proposed for Section 8.2 of the EML**

Imatinib
GASTROINTESTINAL STROMAL TUMOR
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

References


