Background/Introduction

- Gastrointestinal stromal tumors (GISTs) are tumors of the bowel wall that originate in the interstitial cells of Cajal. They represent the most common mesenchymal tumors of the GI tract.
- They carry variable malignant potential depending on their size and mitotic rate. The recurrence rate in patients with high risk tumors can be as high as 50% at 5 years.
- About 85% of these tumors carry an activating mutation in the KIT oncogene, and 3—5% can have a mutation in the gene encoding platelet-derived growth factor receptor ? (PDGFR?).
- Imatinib is a small molecule selective inhibitor of the KIT, PDGFR?, ABL, and BCR-ABL tyrosine kinases. It was initially developed as a targeted agent to treat chronic myelogenous leukemia (CML). In this setting, treatment with imatinib produced a complete hematologic response in nearly all patients through inhibition of the BCR-ABL oncoprotein.
- This drug was first used for a patient with metastatic GIST in 2001 with dramatic response, and was then evaluated in a randomized trial where it induced a sustained objective response in more than half of patients with advanced unresectable or metastatic GIST.
- Use of imatinib for treatment of GIST was then evaluated in the adjuvant setting in the ACOSOG Z9001 Phase III trial. Patients were randomized to 1 year of adjuvant imatinib or placebo after complete resection of GIST tumors greater than 3 cm in size. Patients treated with imatinib had significantly improved recurrence-free survival (RFS) compared with placebo (98% vs 83% at 1 year).
  - However, it was observed after this trial that a significant number of patients relapsed within 1 year after discontinuation of imatinib.
  - This raised the question the optimal duration of imatinib therapy in the adjuvant setting.
- This question was addressed in patients with advanced GIST in a French Phase III trial (BFR14), which compared interruption versus continuation of imatinib treatment beyond 1 year. This study demonstrated that imatinib interruption results in rapid progression in most patients with advanced GIST.
The authors of the study presented here hypothesized that 3 years of adjuvant imatinib would be superior to 1 year of adjuvant imatinib in terms of RFS, and undertook this randomized Phase III study in order to further investigate this question.

Methods

This was a prospective, multicenter, randomized Phase III study which randomized GIST patients 1:1 to 1 year or 3 years of adjuvant imatinib after surgical resection.

Inclusion criteria: patients with histologically diagnosed KIT-positive GIST tumors, at high risk of recurrence according to the Modified Consensus Criteria:

- Tumor diameter > 10 cm, or
- Tumor mitosis count > 10 / 50 HPF (high powered field), or
- Size > 5 cm and mitosis count > 5 / 50 HPF, or
- Tumor rupture spontaneously or at the time of surgery.

Exclusion criteria: inoperable, recurrent, or metastatic disease; ECOG PS > 2; or > 12 weeks between surgery and study entry.

Tumor histology and mutation analysis was centrally reviewed.

Imatinib was administered 400 mg per day orally, although the dose was reduced to 300 mg/day for Grade 3 or 4 non-hematologic toxicity.

The primary objective was recurrence-free survival (RFS). Clinical assessment was by CT or MRI every 6 months, clinical examination, and blood cell counts.

Secondary objectives included overall survival (OS) and toxicity.

The study was powered assuming an overall hazard ratio (HR) of 0.44 in favor of the 3-year group, requiring 400 patients overall.

Analysis was based on the intention-to-treat population (ITT), and was also performed for the "efficacy population" who had confirmed GIST on pathology review and no overt evidence of metastatic disease at study entry.

Results

200 patients were randomly assigned to each group; 397 were included in the ITT analysis; 15 patients had no GIST on central pathology review, and 24 had metastases at study entry and were excluded from the efficacy population, leaving 358 patients.

Discontinuation of assigned treatment occurred in 15% of patients assigned to 1 year of imatinib, and 32% of patients assigned to 3 years of imatinib.

The most common reason for this was "adverse event" in 8% and 14%, respectively; however, it was for "other reasons" in 5% and 12%, respectively.

The 2 arms were well-balanced, and patient characteristics were notable for:
- Gastric primary tumor in ~50% patients in each arm
- Median tumor size ~ 10 cm in each arm
- Median mitosis count was ~ 9 / 50 HPF in each arm
- Tumor rupture in about 20% patients in each arm

- Mutation analysis revealed that most tumors harbored mutations in KIT exon 11 (70%); 9% of tumors were wild type tumors with no detectable mutations in either KIT or PDGFR?.
- With a median follow up of 54 months, RFS (by ITT analysis) favored the 3-year arm, with a 5 year RFS of 66% in the 3-year arm versus 49% in the 1-year arm. The hazard ration (HR) was 0.46 (p < .0001) favoring the 3-year group.

  - RFS in the efficacy group also favored the 3-year group, with the same HR as above.

  - There was an overall survival (OS) benefit in the 3-year group, with a 5-year OS of 92% versus 82% for the 1-year group (p = .019).

  - Tolerability: almost every patient in the study had at least one adverse event recorded, although most of these were Grade 1 or 2.

  - Grade 3 or 4 events were more common in the 3-year group, occurring in 33% of patients compared to 20% of patients assigned to 1 year of imatinib (p = .006)
  - A greater proportion of patients assigned to 3 years discontinued imatinib early for a reason other than GIST recurrence: 26% versus 13% assigned to 1 year (p = .001)

Authors' Conclusions

- Compared to 1 year of adjuvant imatinib, 3 years of adjuvant imatinib improved RFS and OS in GIST patients with a high risk of recurrence after surgery.
- Adjuvant imatinib is well tolerated, and severe adverse events are infrequent.

Clinical/Scientific Implications

- This study establishes that a longer course of adjuvant imatinib (at least 3 years) may be considered standard of care for patients undergoing gross total resection of GIST with a high risk of recurrence after surgery based on pathologic risk factors. This is based on an improvement in RFS and OS with 3 years of drug administration compared to 1 year.
- When examined in the context of other studies, notably the French study (BFR14) of patients with advanced GIST treated with variable durations of imatinib, it is possible that for GIST patients with a high risk of recurrence after surgery, adjuvant imatinib may not be achieving a "cure," but rather a prolonged remission.

  - The implication of this is that if imatinib is discontinued after 3 years, after some period of time the overall survival benefit will be lost as these patients begin to relapse, and eventually die of their disease.
  - Therefore, it is possible that these patients will require an indefinite course of imatinib to remain in remission, and this will require further investigation.

- There are practical concerns with the long-term or indefinite use of imatinib that can be deduced from this study. Namely, the feasibility of achieving long-term compliance with a drug that has low-grade toxicity may be limited by several factors:
● A greater proportion of patients assigned to 3 years of the drug discontinued imatinib early for a reason other than GIST recurrence (26%). A certain percentage of patients would also be expected to discontinue the drug on an indefinite regimen, although this has not been studied explicitly.

● Another practical consideration with indefinite imatinib maintenance in the adjuvant setting is the high cost of this regimen.

● Long-term follow-up is needed to determine whether the overall survival benefit demonstrated here persists over time in patients in whom imatinib has been discontinued after 3 years, as this will give provide insight into whether cure is truly being achieved. Late relapses may promote investigation of longer-term or indefinite use of imatinib.