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Phase II trial of adjuvant imatinib mesylate after resection of localized, primary high risk gastrointestinal stromal tumour (GIST) in Japan

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Background: Pts with high-risk GIST frequently relapse even after complete surgical resection. Although imatinib is active for advanced GIST, cure can not be obtained by imatinib alone. To reduce the risk of relapse after GIST surgery, multi-modality treatment approaches including imatinib adjuvant therapy is required. In this study, efficacy and safety of imatinib as adjuvant therapy for Japanese GIST pts are examined.
Methods: A single arm, open-label, multi-center trial conducted in 17 hospitals in Japan. The eligibility criteria included a diagnosis of histologically proven primary high-risk GIST and having undergone macroscopically complete resection. High-risk was defined according to NIH consensus as either tumor size > 5 cm with mitotic count >5/50 HPF, tumor size >10 cm or mitotic count >10/50 HPF. Pts were treated with imatinib 400 mg/day for 1 year after surgical resection. The primary endpoint was relapse-free survival, the secondary endpoints were overall survival and safety. The study is registered with Clinical Trials.gov, number NCT00171977 and sponsored by Novartis.
Results: 64 pts were enrolled between Sep 2004 and Jul 2006. The median age was 60 years, with 41 (64%) males. The median size of the tumor was 9.0 cm, and the median mitotic count was 14.5/50 HPF. 40 tumors locate in the stomach (63%), 16 small intestine (25%), and 8 include the esophagus and colorectal. Oncogenic mutations were detected in c-*kit* exon 9 (n = 6), exon 11 (n = 49), exon 17 (n = 1), *PDGFRA* exon 12 (n = 2), exon 18 (n = 1) and wild type (n = 3). 49 (77%) pts completed one-year treatment; 15 (23%) pts did not complete due to relapse (n = 2), toxicities (n = 10), and consent withdrawal (n = 3). The 2 pts relapsed during treatment exhibited c-*kit* exon 9 mutation and wild type, their primary sites were small intestine and stomach, respectively. With a median follow-up of 109 weeks (range, 0 to 150 weeks), 20 pts have had relapse and the 3-year relapse-free and overall survival rates were 59% and 87%, respectively. All pts experienced drug-related mainly minor adverse events. The most frequent toxicities of any grade were eyelid edema (44%), nausea (39%), rash (38%), neutropenia (38%) and face edema (36%). 19 (30%) pts had grade 3−4 toxicities, including neutropenia (13%), hypophosphataemia (6%) and rash (3%).
Conclusions: Adjuvant therapy with imatinib 400 mg/day for 1 year is highly effective to reduce risk of relapse and well tolerated for Japanese high-risk GIST pts.

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Study on clinical biological characteristics and prognostic factors in 89 patients with gastrointestinal stromal tumor of the small intestine

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Background: GISTs originating from small intestine have more insidious clinical progression and non-specific manifestation than those from stomach. They are difficult to be early detected and diagnosed with conventional methods. Until now, only a few studies were focused on them. This study aimed to identify the factors which were associated with tumor recurrence and disease free survival (DFS) in patients with small intestine GISTs.
Materials and Methods: From January 2003 to September 2007, 89 patients were enrolled after completely resected operation in Ruijin Hospital. All patients were classified into three groups (low risk, intermediate risk and high risk) by using the risk criteria for aggressive behavior defined by NIH which is based on the tumor size and mitotic rate per 50 high power field.
Results: There were 44 male (49.4%) and 45 female (50.6%) patients. They had a median age of 55 years (ranging from 21 to 81 years). The mean tumor diameter was 4.0 cm (rang from 2.0 to 11.2 cm). Tumor diameter was between 2 and 5 cm in 52 cases, between 5 and 10 cm in 30 cases and larger than 10 cm in 7 cases. According to the Fletcher risk classification system, 46 patients (51.7%) were classified at low risk, 26 (29.2%) at intermediate risk and 17 (19.1%) at high risk group. The positive rate of CD117 was 100%. Among 89 patients, 58 cases were detected by double-balloon enteroscopy (DBE) and 31 cases were detected by multi-slice spiral CT enteroclysis (MSCTE). The diagnostic yield of DBE and MSCTE was 90.6% (58/64) and 88.6% (31/35), respectively. After a median follow-up period of 32 months (ranging from 12 to 67 months), recurrence was noted in 15 patients (16.9%) with a median time of 19 months (ranging from 7 to 47 months). There were 9 patients (10.1%) who died of GIST with a median time from recurrence to death of 13 months (ranging from 8 to 20 months). Based on single-and multi-variate survival analysis, size and mitotic rate of tumor were independent risk factors for patients' DFS ($p < 0.05$).
Conclusions: DBE with combination of MSCTE could have the entire small bowel scrutinized clearly and directly, which was the most accurate, highest diagnostic yield modality to small intestinal GISTs. The size and mitotic rate of small intestinal GISTs were independent prognostic factors and showed significant association with patients' DFS.

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Malignant gastrointestinal stromal tumours treated with imatinib in France: results in unselected patients

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Background and Objectives: GISTs are rare tumors of the GI tract. In France, their incidence is estimated to be $9-12/10^6$ inhabitants/year. Imatinib (IM) has been approved to treat unresectable and/or metastatic Kit-positive GISTs since 2002 but information on routine use, safety and efficacy in unselected "real life" setting is lacking. An observational cohort (EPIGIST) in France was designed to provide data on survival, safety and treatment patterns and quality of life.
Methods: EPIGIST is a nationwide multi-center, observational study on GIST patients (pts) treated with IM for the first time between the availability on the French Market and the end of the 2008. Centers were randomly selected in national files of oncologists, gastrointestinal surgeons and gastrointestinal specialists. The planned follow-up duration was three years. A case report form (CRF) had to be completed at inclusion and during each follow-up visits. Quality of life was assessed using QLQ-C30 and SF36 questionnaires.
Results: 30 on 51 selected centers enrolled at least one pt and 135 pts were included (as of 02/2009), The median age of disease onset was 58 years (range 21−86) with 42% pts>60 years. 42% were metastatic at diagnosis. Primary tumors were most often stomach (48%), or from duodenum/jejunum/ileum (34%). At diagnosis 86% of pts had a tumor size over 5 cm. 68% of pts were considered as high risk according the Miettinen classification. 68% of patients had surgery of the primary tumor before starting IM. For 99% of the pts, IM was given at an in initial dosage of 400 mg, 1% at 300 mg. Compliance was superior to 90% for 99% of pts. With a median follow-up of 2.1 years, two-years overall survival from first treatment with IM was 83.9% (95% CI: [74.5−90.1%]).
Conclusion: EPIGIST is still an ongoing survey. Current results confirm previous published data on survival in GIST treated with IM in an unselected cohort of patients outside of a clinical trial.