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Long-term Survival on S0033 − a Phase III Randomized, Intergroup Trial Assessing Imatinib Mesylate at Two Dose Levels in Patients With Unresectable or Metastatic Gastrointestinal Stromal Tumours (GISTs)

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Background: S0033 was a large-scale, open label randomized phase III trial assessing two doses of imatinib mesylate in advanced GIST patients. Early analysis demonstrated equivalent progression-free survival (PFS) for patients treated with standard- or high-dose drug therapy. This analysis describes the updated median survival for patients on both arms of S0033, as well as long-term outcomes for participants.
Materials and Methods: Patients with metastatic or surgically unresectable GISTs were eligible for the original clinical trial. Patients were randomly assigned to imatinib mesylate, at 400 mg once or twice daily, with close interval follow-up. Non-progressing patients without significant toxicities were allowed to stay on imatinib indefinitely, and ongoing results were monitored.
Results: Between December 15, 2000 and September 1, 2001, seven hundred forty-six patients with advanced GISTs, from 148 centers across the United States and Canada, were enrolled onto this trial. Six-hundred ninety-five were eligible. No new long-term toxicities emerged in this analysis. Median survival was 54 months for patients treated with imatinib at 400 mg/d and 51 months for those given 800 mg. With median follow-up of 8.8 years for all survivors, one-hundred thirty-six patients were known to be alive for at least eight years. The table below lists minimum overall survival by time increment, for the longest known living patients:

Table: Minimum overall survival for longest known living patients

Years	% of Patients	95% CI
8	31	27−34
9	26	23−29
10	21	17−25

Survivors of $\geqslant$8 years were seen in multiple demographic groups, including: all ages (40->70 years), both genders, PS 0−3, and those with objective responses and stable disease. There was no difference in percentage of long-term survivors according to treatment dose.
Conclusions: Though median progression-free survival for advanced GIST patients treated with imatinib is only two years and most still die from their disease, this trial demonstrates a significant subset does substantially better. The 8-year Kaplan–Meier overall survival estimate is 31%. S0033 is the first large-scale cooperative group randomized study demonstrating selected advanced GIST patients treated with imatinib alone experience survival without progression for periods that approach and even exceed one decade, with no emerging long-term toxicities. A description of factors associated with long-term survival will be available summer of 2011.

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Cell-cycle Activity is Correlated With Aggressiveness and Prognosis of Gastrointestinal Stromal Tumours

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Background: Multidisciplinary treatment for advanced gastrointestinal stromal tumours (GIST) requires proper prognostic stratifications. Now, size, mitosis and locus are of prognostic importance for GIST. Proliferative activities may reflect biological aggressiveness, but, other than mitosis, no reliable factors have been reported except a few immunohistochemical studies (IH). Here, we analyzed cell cycle activities and evaluated biological and prognostic values of CDK activities.
Methods: 68 pts with primary and histologically proven GIST underwent R0 surgery between July 2004 and Dec 2009 were included. Median age was 60 yrs, median follow-up 37 months, and 31 (46%) pts were male. Using frozen samples, expression and specific activities of CDK1 and CDK2 were measured and genotyping was done.
Results: Risk stratification included 1 very low, 28 low, 18 intermediate, and 21 high risk GIST. Location included 49 gastric GIST, 17 small intestinal and each one of colonic and other. KIT and PDGFRA mutations were found in 56 and 7 GIST pts, respectively, and deletion of KIT codon 557–558 in 17 pts. Two pediatric and one NF-1 GIST had no mutation in both genes. CDK activities were measurable in 59 (87%) pts, and median specific activities of CDK1 and CDK2 were 19 U and 81, respectively. CDK2 activity was significantly related to mitosis, Ki67, pathological necrosis, KIT deletion mutation, clinical symptoms, invasion, rupture, and size, among which mitosis and Ki67 were independently correlated with CDK2 in multiple regression analysis. CDK1 activity was slightly related with deletion mutation and invasion, and their protein levels were not correlated with any clinicopathological factors. During follow-up, 19 recurrences and 7 deaths were observed. Size (> or <5 cm; $p = 0.0005$), loci (gastric or non-gastric; $p = 0.0001$), mitosis (> or <5/50HPF; $p = 0.0024$), rupture ($p = 0.0039$), pathological necrosis ($p = 0.0008$), deletion mutation ($p = 0.0041$), and CDK2 activity ($p = 0.0006$) were significantly related to recurrence. Expression of CDK1 and CDK2 proteins had no correlation with RFS and OS. In Cox regression analysis, only mitosis ($p = 0.0391$) and CDK2 activity ($p = 0.0003$) were significantly related with RFS.
Conclusions: CDK2 activity may correlate with clinical, pathological, and genetic aggressiveness of GIST and also related with RFS. Thus, analysis of cell cycle activity may be useful for prediction of relapse in GIST and candidates for multidisciplinary treatment.

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Can Serum D-dimer Monitoring Reduce the Frequency of Radiological Assessment in Patients Receiving Palliative Imatinib for Gasto-intestinal Stromal Tumour (GIST)?

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Introduction: Current guidelines suggest that CT scans be performed every three months to monitor for progression in patients being treated with imatinib for metastatic GIST [1,2]. We aimed to examine how reliably d-dimer measurement can reduce the requirement for this intensive schedule of imaging. D-dimer levels have been shown to reflect disease activity in a number of cancer types. We have been monitoring d-dimers in patients with GIST for 10 years. We therefore assessed the use of d-dimer monitoring as a biomarker to predict non-progression in GIST.
Patients and Methods: Patients treated with palliative imatinib for GIST in a single tertiary centre were retrospectively identified using a systematic search of an electronic clinical database. Whilst treated with imatinib, patients were assessed three monthly with CT scanning and d-dimer measurement using the HemosIL HS assay. The change between the two consecutive d-dimer levels prior to a CT scan was calculated irrespective of the time interval between samples. This was assessed for its ability to predict or rule-out radiological progression (rPD) using radio operator curve (ROC) analysis.
Results: 51 patients treated between 1st Jan 2000 and 1st Jan 2010 met criteria for inclusion. In total there were 385 separate 3-month observation points of which 80 identified rPD, giving a pre-test probability of rPD of 21%. The post-test probabilities of rPD were 11% for a falling d-dimer level and 38% for a d-dimer rising by at least 100. A rising d-dimer level prior to a CT scan was associated with rPD (odds ratio for rPD 2.1; 95% CI 1.3−3.5; $p = 0.003$). The optimal magnitude of change in d-dimer level to exclude rPD was identified by ROC analysis as a fall of at least 100. A fall of at least this magnitude was seen in 18% of observations and had a negative predictive value for rPD of 85%.
Conclusion: D-dimer monitoring can inform the scan probability of GIST progression during imatinib treatment in a useful proportion of cases. In such patients the frequency of CT scanning may be reduced without a significant risk of not detecting tumour progression. Implications include cost reductions and a lesser burden for patients.

References

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