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Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: A prospective randomised trial in China

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Abstract ***Objectives:*** For advanced gastrointestinal stromal tumour (GIST) patients who are responding to imatinib mesylate, the role of surgery has not been formally demonstrated. This multicenter randomised controlled trial was designed to assess whether surgery to treat residual disease for patients with recurrent/metastatic GISTs responding to imatinib mesylate (IM) improved progression free survival (PFS) compared with IM treatment alone.

Methods: Between 3 and 12 months after starting IM for recurrent/metastatic GISTs, eligible patients were randomised to two arms: Arm A (surgery for residual disease) and Arm B (IM treatment alone). In Arm A (19 pts), surgery was performed to remove residual macroscopic lesions as completely as possible, and IM treatment continued after surgery. In Arm B (22 pts), IM was given alone at a dose of 400 mg per day until disease progression. The primary end-point was PFS measured from the date IM started. This study was registered in the ChiCTR registry with the ID number ChiCTR-TRC-00000244.

Results: This randomised trial was closed early due to poor accrual. Only 41 patients were enrolled as opposed to 210 patients planned. 2-year PFS was 88.4% in the surgery arm and 57.7% in the IM-alone arm ($P = 0.089$). Median overall survival (mOS) was not reached in the surgery arm and 49 months in patients with IM-alone arm ($P = 0.024$).

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Conclusions: While no significant differences were observed in the two arms, this study suggests that surgical removal of the metastatic lesion may improve the outcome of advanced GIST patients and should stimulate additional research on this topic.

1. Introduction

Gastrointestinal stromal tumours (GISTs) are the most common sarcoma of the abdomen. In pre-imatinib era, surgery was the only effective treatment for GISTs. Five-year survival rate for patients with GISTs ranged from 28% to 80%. Yet tumour progression developed in approximately 50% of patients, even after complete resection. Among patients with recurrent and/or metastatic GISTs, the median survival period was 6–18 months [1,2]. Dramatic improvement in GIST management occurred by recognising that mutational activation of KIT or platelet-derived growth factor receptor alpha (PDGFRA) stimulated the growth of these cancer cells. This had led to an effective therapy with small-molecule tyrosine kinase inhibitor imatinib mesylate (IM) [3,4].

The major limitation of this active drug is the development of secondary resistance, mainly due to the development or selection of acquired mutations [5,6]. Long-term complete remissions remain a rare exception, especially in patients with metastatic GIST treated with IM. To date, there is an undefined role for surgery in the management of these patients. Recent single-institution series have explored the possible role of surgery in combination with IM [7–9]. These series consistently show that surgery can be safely combined with IM treatment in recurrent and/or metastatic GIST patients, and better results can be obtained if surgery is performed on patients with stable responsive disease. However, there is a lack of any randomised trial to validate the role of surgery. In order to prove the benefit of surgery in this setting, a randomised, controlled clinical trial was designed in China to evaluate the role of surgery for patients with recurrent/metastatic GISTs responding to IM.

2. Materials and methods

2.1. Patients

Patients with histologically confirmed, CD117 positive, recurrent and/or metastatic gastrointestinal stromal tumours were eligible. In addition, patients were required to meet the following criteria:

1. no prior treatment with imatinib or other tyrosine kinase inhibitors in the adjuvant or neo-adjuvant setting;
2. treatment with IM administered for 3–12 months resulting in complete response (CR)/partial response (PR) or stable disease (SD) by computed tomography (CT)/magnetic resonance imaging (MRI) scan;
3. surgically resectable residual disease after surgical assessment, which has to be made on CT/MRI scan performed within 14 days prior to randomisation;
4. age $\geqslant$18 years;
5. absence of extra-abdominal metastases;
6. measurable or evaluable lesion, according to Response Evaluation Criteria in Solid Tumours (RECIST);
7. performance status of 0 or 1 by the Eastern Cooperative Oncology Group criteria;
8. adequate liver, kidney and bone marrow functions.

Patients were excluded for one or more of the following reasons: tumour progression; severe and/or uncontrolled concurrent medical disease; prior malignancy; financial or logistical barriers to completing the trial and refusal of informed consent.

All patients signed written consent according to ICH/GCP.

2.2. Trial design

This was a randomised, multicenter, Phase III, controlled trial, performed in China. Eligible patients were within 3 to 12 months of starting molecular-targeted therapy of IM at a dosage of 400 mg per day for recurrent/metastatic disease, careful evaluations were performed by the responsible surgeon based on CT/MRI scan within 2 weeks before randomisation. The disease would be confirmed in response (defined as CR, PR and SD as compared to the original disease, before imatinib onset) within the same time period. Patients with surgically resectable residual disease after assessment were randomised to two arms using 1:1 randomisation: Arm A (surgery for residual disease plus IM) and Arm B (IM alone).In Arm B (IM alone), IM was administered orally at 400 mg per day until disease progression. In Arm A (surgery for residual disease), surgery was performed as soon as possible, within 4 weeks after randomisation. Resection should therefore encompass all visible disease – if resectable – with the lesser surgical morbidity as possible. IM treatment continued as soon as possible after surgery.

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