Efficacy of surgery and imatinib mesylate in the treatment of advanced gastrointestinal stromal tumor: a systematic review

Cirocchi R, Farinella E, La Mura F, Cavaliere D, Avenia N, Verdeccia GM, Giustozzi G, Noya G, Sciannameo F

CRD summary
This review concluded that neoadjuvant imatinib mesylate associated with surgery significantly improved disease-free and overall survival in patients with complete or partial response to imatinib mesylate. Confusion regarding interventions, comparisons and outcomes rendered the data unusable and unsuitable for drawing conclusions about the role of imatinib mesylate and its association to surgery in advanced gastrointestinal stromal tumours.

Authors' objectives
To investigate the role of imatinib mesylate associated with surgery in unresectable and/or metastatic gastrointestinal stromal tumours.

Searching
MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Current Controlled Trials, Science Citation Index, Conference Proceedings Citation Index and Zetoc. Reference lists of included studies and previous systematic reviews were searched for relevant articles. Search terms were reported.

Study selection
Randomised controlled trials and controlled clinical trials of neoadjuvant imatinib mesylate and surgery compared with surgery alone in patients with unresectable and/or metastatic gastrointestinal stromal tumours were eligible for inclusion. Primary outcomes were overall survival and disease-free survival. Studies were excluded if they did not report the outcomes of interest, if the necessary data could not be calculated from the published results and where there was considerable overlap between authors, centres or patient cohorts.

Application of these inclusion criteria resulted in a lack of controlled trials, so the authors expanded the inclusion criteria to include other study designs. The inclusion criteria were redefined as studies of preoperative imatinib mesylate use in patients with unresectable and/or metastatic gastrointestinal stromal tumours. The primary outcome remained the same. Most of the included trials were from USA and Europe.

Two reviewers selected studies for inclusion. Disagreements were resolved through discussion or consultation with a third reviewer.

Assessment of study quality
The methodological quality of studies was assessed by two independent reviewers. Criteria for validity assessment were not fully reported. Disagreements were resolved by consensus or consultation with a third reviewer.

Data extraction
Two independent reviewers extracted odds ratios (OR) into standard data extraction forms. Disagreements were resolved by consensus.

Methods of synthesis
Pooled odds ratios and corresponding 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel fixed-effect model. Statistical heterogeneity was assessed with $\chi^2$ and $I^2$.

Subgroup analysis investigated responses to imatinib mesylate specifically, complete or partial response and progressive or stationary disease.

Results of the review
No randomised controlled trials or controlled clinical trials were identified for neoadjuvant imatinib mesylate and surgery compared with surgery alone in patients with unresectable and/or metastatic gastrointestinal stromal tumours. Seven observational studies (n=256) were included in the review. One study was prospective and six studies were retrospective.

Significantly more patients in the progressive or stationary disease group had recurrent or metastatic disease than had locally unresectable disease (OR 0.1, 95% CI 0.02 to 0.40).

There were significantly fewer incomplete resections in the complete or partial response disease group compared with the progressive or stationary disease group (OR 0.06, 95% CI 0.03 to 0.11).

Recurrence within 24 months of imatinib treatment and complete resection was significantly less common in the complete or partial response group, compared with the progressive or stationary disease group (OR 0.13, 95% CI 0.03 to 0.50).

Overall survival within 24 months of imatinib treatment and complete resection was significantly improved in the complete or partial response group compared with the progressive or stationary disease group (OR 0.04, 95% CI 0.00 to 0.37).

**Authors' conclusions**
In advanced gastrointestinal stromal tumours, the advantages of neoadjuvant imatinib mesylate associated with surgery were significant in the complete or partial response disease group in terms of more complete resections and better disease-free and overall survival.

**CRD commentary**
This review initially addressed a clear question supported by appropriate inclusion criteria. The authors made a reasonable effort to minimise reviewer error and bias. The search revealed no controlled trials to answer the initial question and the authors were prompted to consider other study designs and amend their inclusion criteria. These amended criteria were not well described and it was unclear how studies were selected. Outcome measures were not predefined. The authors did not report any methods they used to minimise reviewer error and bias for this new set of criteria.

Relevant databases were searched without language restrictions and attempts were made to identify unpublished data. It was unclear up to which date the searches were conducted. Publication bias was not considered in the report.

Statistical analysis of the data was not appropriate. Instead of reporting the outcome measures as a function of the intervention, the authors reported outcomes as a function of various patient subgroups. Data presented for recurrence within 12 months of imatinib treatment incorrectly claimed a significant difference between complete or partial response and progressive or stationary disease subgroups (OR 0.1, 95% CI 0.01 to 1.12).

The confusion regarding interventions, comparisons and outcomes rendered the data unusable and unsuitable for drawing conclusions about the role of imatinib mesylate and its association to surgery in advanced gastrointestinal stromal tumours. The authors' conclusions are unlikely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that for patients who responded to imatinib or patients with prolonged stable disease, resection of residual disease should be considered if the tumour become resectable. In general, surgery should be planned when the maximal response to molecular-targeted therapy was reached. This usually happened within six to 12 months after onset of TKI (tyrosine kinase inhibitor) therapy. Surgery should be considered for patients at higher risk of complications during pharmacological debulking. These implications were inappropriate since the review did not assess these outcomes.

**Research:** The authors did not state any implications for further research.
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