Imatinib as adjuvant therapy for gastrointestinal stromal tumors: a systematic review
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CRD summary
This well-conducted review found some evidence that adjuvant treatment with imatinib improved recurrence-free survival in patients with KIT-positive gastrointestinal stromal tumours after surgical resection. The authors’ conclusions about the results and the requirement for further well-designed trials are likely to be reliable.

Authors' objectives
To assess the clinical efficacy and safety of imatinib for the adjuvant treatment of adult patients with localised KIT-positive gastrointestinal stromal tumours after complete resection, compared to current standard therapy.

Searching
MEDLINE, EMBASE, Science Citation Index, DARE, The Cochrane Library and research registers were searched without language restrictions to August 2009; search terms were reported. The authors checked conference proceedings and reference lists of included studies for additional studies. Contact was made with experts to identify further studies.

Study selection
Studies of any design in which imatinib as adjuvant therapy was evaluated in patients 18 years or older with surgical resections for KIT-positive gastrointestinal stromal tumours were eligible for inclusion. The outcomes of interest were progression or recurrence-free survival, overall survival, recurrence rates, adverse effects of treatment and health-related quality of life.

The patients in the included trials presented with high risk gastrointestinal stromal tumours. Surgical treatments included complete resections of gastrointestinal stromal tumours, mucosal sleeve resections, radical surgery, laparoscopic wedge resections and partial gastrectomy. Tumours ranged in size between 3cm and 42cm. Imatinib was administered at a dose of 400mg/daily post surgery. In some studies the dose of imatinib was increased to 600mg per day due to tumour recurrence and in some other studies the daily dose of imatinib was decreased to 200mg to 300mg per day because of side effects of treatment. Control groups received placebo or no treatment following surgery. Where reported, treatment duration ranged from 12 to 41 months and follow-up ranged from 12 months to 62 months. Paper in languages other than English were excluded from the review.

It appeared that one reviewer performed the study selection and if there was any doubt regarding inclusion, the paper was checked by a second reviewer; any disagreements were resolved by discussion.

Assessment of study quality
Methodological quality of randomised trials was evaluated using criteria proposed by the Centre for Reviews and Dissemination for randomisation, concealment, blinding, losses to follow-up and use of intention-to-treat analyses. The Critical Appraisal Skills Programme checklist was used for assessment of non-randomised studies. There was no assessment of quality for case reports.

It was not clear how many reviewers performed the quality assessment.

Data extraction
Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Numbers needed to treat (NNT) were calculated for the primary outcome.

Data were extracted by one reviewer. Accuracy was checked by a second reviewer. Any disagreements were resolved by discussion.

Methods of synthesis
The results of the review were summarised in a narrative synthesis and grouped according to study design. Differences between the studies were evident from the tables.
Results of the review

Sixteen uncontrolled phase II studies (1,110 participants) were included in the review: one randomised controlled trial (RCT, 713 participants), three phase II studies (204 participants), three cohort studies (181 participants) and nine case reports (12 participants). The RCT was described by the reviewers as being of good quality, with appropriate randomisation and blinding and use of intention-to-treat analyses. Adequate methods of recruitment were reported in the uncontrolled studies and more than 80% of the participants were included in the follow-up; in these studies it was unclear whether confounding factors were identified by the study authors.

The results of the RCT showed significant benefits of adjuvant treatment with imatinib, with a 65% reduction in the risk of disease recurrence at one year (HR 0.35, 95% CI 0.22 to 0.53) with a NNT of seven patients to prevent one recurrence or death from gastrointestinal stromal tumours. In each tumour size category, recurrence-free survival was higher in the imatinib-treated groups.

No differences in survival were observed between the imatinib-treated group and the placebo-treated group in the RCT. There were significantly larger numbers of early withdrawals from treatment in the imatinib-treated group than the placebo-treated group (16% in the imatinib group compared to 3% in the placebo group, p<0.0001). Withdrawals due to tumour recurrence were higher in the placebo-treated group (12%) compared to the group of patients who received imatinib (<1%). The most common adverse events in the imatinib-treated group were dermatitis, abdominal pain and diarrhoea.

The other studies showed trends towards increased recurrence-free survival in patients treated with adjuvant imatinib therapy.

Authors’ conclusions

There was some evidence that use of adjuvant treatment with imatinib improved recurrence-free survival in patients with resected localised KIT-positive gastrointestinal stromal tumours. The treatment was associated with a reasonable tolerability profile.

CRD commentary

The review addressed a question that was broad in scope and the stated criteria for inclusion reflected this. Appropriate databases were searched for relevant studies. There were no language or publication restrictions and there were attempts to identify unpublished studies. The authors stated that the review was restricted to articles published in English, which meant there was a risk of language bias, although they stated that most of the studies in other languages were single case reports. Steps were taken to minimise errors and bias in study selection and data extraction, but were not explicitly reported for the assessment of methodological quality. The methods used to assess methodological quality were appropriate.

The authors’ decision not to combine the results of the studies was justified, given the heterogeneity in study designs and the likelihood of potential biases associated with the results of uncontrolled studies.

The review was funded by Novartis, the manufacturer of imatinib.

The review was generally well conducted and the authors’ conclusions about the results and the requirement for further well-designed trials are likely to be reliable.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research was required to confirm the results of the review and provide additional information on overall survival, health-related quality of life, benefits of maintenance therapy, survival after the withdrawal of imatinib treatment, drug resistance in recurrent gastrointestinal stromal tumours and the optimum treatment duration of imatinib as adjuvant therapy.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.