Incidence and risk of congestive heart failure in patients with renal and nonrenal cell carcinoma treated with sunitinib

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CRD summary
This review found an increased risk of congestive heart failure in patients who were treated with sunitinib for cancer. A limited search and the possibility of biases in the search process make the reliability of the authors’ conclusions unclear.

Authors’ objectives
To evaluate the risk and incidence of congestive heart failure in patients receiving sunitinib therapy for cancer.

Searching
MEDLINE was searched from January 1966 to February 2011 for relevant studies in English; search terms were reported. Researchers were contacted to identify additional studies. The most recent package insert was checked for the most recent clinical information.

Study selection
Phase II and Phase III studies and expanded access protocols of patients with cancer treated with sunitinib that included sufficient safety data for assessment of congestive heart failure were eligible for inclusion. The reviewers included left ventricular ejection fraction decreases and congestive heart failure not otherwise specified as adverse events. Studies that did not report congestive heart failure events or regular cardiac monitoring were excluded from the review. Meeting abstracts, review articles, letters and reports on study designs were excluded from the review.

Patients in the included trials presented with renal cell carcinoma, gastrointestinal stromal tumours, prostate cancer, pancreatic cancer, HER2-negative breast cancer, colorectal cancer, cervical cancer and uterine leiomyosarcoma. Patients with histories of clinically significant cardiovascular disease or dysrhythmias, prolongation of the QT interval or uncontrolled hypertension were generally excluded from individual trials. Sunitinib was administered at doses that ranged from 37.5mg to 50mg on days one to 28 every six weeks in most of the studies. In the randomised controlled trials (RCTs) the comparators were placebo, interferon immunotherapy and capecitabine administered at doses of 1,250mg/m² twice daily on days one to 14 every three weeks. Outcomes evaluated were incidence of all congestive heart failure events and incidence of high-grade congestive heart failure events. Treatment duration ranged from 0.03 to 37.5 months.

Three reviewers performed the study selection; any discrepancies between reviewers were resolved by consensus.

Assessment of study quality
Methodological quality of the RCTs was assessed with the Cochrane risk of bias tool, Jadad scale and the Newcastle-Ottawa scale by three independent reviewers. The quality components evaluated were randomisation, allocation concealment, comparability of control groups, use of blinding, losses to follow-up, use of intention-to-treat analyses and the extent to which the study was free from selective reporting. Non-randomised studies were evaluated using the Newcastle-Ottawa scale only.

Data extraction
Data were extracted by three independent reviewers to calculate relative risks (RR) and 95% confidence intervals (CI) for the outcomes. Incidence rates were calculated.

Methods of synthesis
Summary incidence rates, pooled relative risks and 95% CIs were calculated using a fixed-effect model. Statistical heterogeneity between the trials was assessed using Cochran's Q-statistic and I² test. Where substantial statistical heterogeneity was present, pooled estimates were calculated using random-effects models. Subgroup analyses examined the effect of use of regular cardiac monitoring, renal cell carcinoma compared to other cancers and trials with short or long progression-free survival periods. The reviewers evaluated publication bias using visual appraisal of funnel plots.
Results of the review

Sixteen studies (6,935 patients) were included in the review: four Phase III studies/RCTs, 11 Phase II trials and one expanded access protocol. Median progression-free survival ranged from 1.5 months to 11.5 months. One RCT scored 5 on the Jadad scale and three scored 3.

In all the studies, congestive heart failure events regardless of grade occurred in 186 patients (total incidence of 4.1%, 95% CI 1.5% to 10.6%; 12 RCTs). High grade events occurred in 44 patients (incidence of 1.5%, 95% CI 0.8% to 3.0%; 16 trials).

Four RCTs were included in the meta-analysis and found significantly higher risks observed for developing congestive heart failure in patients with cancer who were treated with sunitinib compared to placebo or control treatments (RR 1.81, 95% CI 1.30 to 2.50; 1,715 patients) with some heterogeneity ($I^2=34.8\%$). There was also a significantly higher risk of high-grade congestive heart failure events in patients with cancer who were treated with sunitinib compared with placebo or control treatment (RR 3.30, 95% CI 1.29 to 8.45; $I^2=0\%$, four studies, 1,692 patients).

No significant differences were observed between groups in subgroup analyses for renal cell carcinoma compared to other malignancies, use of regular cardiac monitoring in the trials and trials with long progression-free survival periods compared to those with short progression-free survival periods.

There was no evidence of publication bias shown for all the outcomes evaluated.

Authors' conclusions

Treatment of patients with cancer with sunitinib was associated with increased risk of developing congestive heart failure.

CRD commentary

The review addressed a clear question and broad criteria for the inclusion of studies were outlined. The limited search (one database) meant that relevant studies may have been missed. The restriction to studies in English published in peer-reviewed journals risked language and publication biases. Steps were taken to avoid reviewer errors and bias at each stage of the review process.

Different cancer types and a lack of information on staging made it hard to know whether it was appropriate to combine the results of the studies. It was unclear what medications the patients may have received previously for cancer that may have had an impact on cardiac function. Appropriately the reviewers did not combine the results of the included Phase II and Phase III studies. There was a discrepancy between tables and text in reporting of the primary outcome of incidence and risk of congestive heart failure.

The limited search and possibility that studies may have been missed make the reliability of the authors' conclusions unclear.

Implications of the review for practice and research

Practice: The authors stated that this drug was used increasingly in clinical practice and physicians should be aware of this adverse event to balance therapeutic benefit with life-threatening adverse events.

Research: The authors stated that it remains to be determined whether congestive heart failure in patients treated with sunitinib was a dose-dependent or reversible effect.

Funding

Trust Family Research Fund for Kidney Cancer.
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.