Risk of bleeding with vascular endothelial growth factor receptor tyrosine-kinase inhibitors sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials

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CRD summary
This review concluded that treatment with sunitinib and sorafenib was associated with a significant increase in risk of bleeding. The authors’ conclusion appeared to reflect the evidence, but should be interpreted with caution due to the questionable quality of the primary studies and some methodological problems in the review.

Authors’ objectives
To calculate the incidence and relative risk of bleeding associated with the use of sunitinib and sorafenib.

Searching
PubMed was searched from 1966 to April 2009 for English-language studies; search terms were reported. Abstracts and virtual meeting presentations from the following conferences (between 2004 and April 2009) were searched: American Society of Clinical Oncology and European Society of Medical Oncology. The manufacturer’s information for the drugs was reviewed.

Study selection
Prospective phase 2 and 3 trials and expanded-access programmes that assessed bleeding associated with the use of sunitinib or sorafenib in patients with cancer were eligible for inclusion. Events regarded as bleeding included: ecchymosis; epistaxis; haematuria; haemoptysis; haemothorax; melaena; purpura; and eye, gastrointestinal, gum, rectal, central nervous system and vaginal haemorrhage.

Participants in the included studies had a variety of different cancers; severity of disease was not reported. Median ages of participants in the included studies ranged from 52 to 75.3 years. The proportion of males and females was not reported. Dosage regimes were sorafenib 400mg twice daily and sunitinib 37.5mg daily or 50mg daily for four weeks then two weeks off. One study added another drug (interferon) to the treatment regime. Median treatment duration ranged from 1.5 to 10.1 months (where stated). In studies that had a comparator, this was placebo or interferon. A variety of bleeding outcomes was reported; these were classified as high-grade (grade 3 or above) or all-grade according to National Cancer Institute’s common toxicity criteria version 2 or 3.

Two reviewers selected studies for inclusion. It was not reported whether selection was undertaken independently and how any disagreements were resolved.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Incidences and 95% confidence intervals (CIs) were calculated for all-grade and high-grade bleeding events in each study. Relative risks (RR) and 95% CIs were calculated for studies with a comparative group. The most recent or complete report was included when duplicate publications were identified.

Two reviewers abstracted data for the review. Disagreements were resolved by consensus.

Methods of synthesis
Incidences and relative risks with corresponding 95% CIs were pooled using both fixed-effect (inverse variance weighted) and random-effects (DerSimonian and Laird) models. It was not reported which model was presented. Heterogeneity was assessed using the Q statistic and quantified using the I² statistic; a p value of 0.10 was used to determine the presence of heterogeneity. Possible sources of heterogeneity were investigated by subgroup analyses.
Meta-regression was planned to assess the variability due to these variables, but was not reported. Publication bias was assessed by funnel plots and with Egger and Begg tests (significance at p<0.05).

**Results of the review**

Twenty three studies were included in the review: four phase 3 randomised controlled trials (RCTs) (n=2,540); 17 phase 2 case series (n=1,352); and two expanded-access case series (n=4,102). Sample sizes ranged from 16 to 2,954. Studies were reported as being full-text, abstract or presentation slides; the method of reporting for each study was not provided.

**Incidence**

Incidence of all-grade bleeding events was 16.7% (95% CI 12.7 to 21.5; 17 studies). Incidence of high-grade events was 2.4% (95% CI 1.6 to 3.9; 18 studies). There was evidence of significant heterogeneity ($I^2>78\%$, p<0.0001 for both analyses). Subgroup analyses found a significantly higher incidence of all-grade bleeding events among sorafenib trials that included renal-cell cancer patients (20.6%, 95% CI 14.1 to 29.2) compared with non-renal-cell cancer patients (7.6% 95% CI 5.4 to 10.5, p=0.018). No other differences between subgroups were found.

**Relative risk**

Sunitinib and sorafenib were associated with a statistically significant increase in the risk of all-grade bleeding compared to placebo or interferon (RR 2.0, 95% CI 1.14 to 3.49, p=0.015; four RCTs). There was no statistically significant difference between the groups for high-grade bleeding events (four RCTs). There was evidence of significant heterogeneity ($I^2=81.7\%$, p<0.0001) for all-grade events, but not for high-grade events. Subgroup analyses found no statistically significant differences.

There was no evidence of publication bias for any of the analyses.

**Authors' conclusions**

Treatment with sunitinib and sorafenib was associated with a significant increase in risk of bleeding.

**CRD commentary**

The review addressed a clear question. Inclusion criteria were defined in terms of intervention; broad criteria were applied to participants, outcomes and study design. The authors searched only one database plus some conference proceedings, so it was possible that some relevant studies were missed. Only English-language studies were included, so there was a possibility of language bias. Publication bias was reportedly not detected. The authors appeared to use methods designed to reduce reviewer bias and error for study selection and extraction of data. The authors did not report conducting an assessment of study validity, which made it difficult to assess the reliability of included studies and data derived from them. Insufficient study details were provided to allow the reader to perform their own assessment of study quality and to assess the generalisability of the results. The study designs included and the lack of quality assessment could indicate a low level of evidence. A few inconsistencies in the review included a mismatch in the reporting of the total number of participants included and planned meta-regression that was not reported. The authors' decision to pool the results in a meta-analysis may not have been appropriate given clinical and statistical heterogeneity and different study designs.

The authors' conclusions appeared to reflect the evidence, but should be interpreted with caution due to the questionable quality of the primary studies and some methodological problems in the review.

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

The authors did not state any implications for practice or further research.

**Funding**

None.

**Bibliographic details**

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.