Risk of hand-foot skin reaction with sorafenib: a systematic review and meta-analysis
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CRD summary
This review aimed to determine the risk of hand-foot skin reaction (HFSR) in patients taking single agent sorafenib. The authors concluded that sorafenib was associated with a significant risk of developing HFSR in patients being treated for advanced solid tumours, particularly renal cell carcinoma. The review suffered from some limitations, but the overall conclusion was likely to be reliable.

Authors' objectives
To determine the risk of hand-foot skin reaction (HFSR) in patients taking single agent sorafenib.

Searching
PUBMED (January 1996 to July 2007) and Web of Science were searched. Search terms were reported. Abstracts presented at the American Society of Clinical Oncology (ASCO) annual meetings from 2004 to 2007 and the ASCO Prostate Cancer Symposium were searched manually.

Study selection
Eligible studies needed to meet the following criteria: prospective clinical trials in cancer patients; participants treated with sorafenib as a single agent at a starting dose of 400 mg twice a day; and data that reported on the outcome of HFSR. Phase I trials were not eligible for inclusion.

Most included studies were uncontrolled trials of sorafenib. Others were controlled trials that compared sorafenib with placebo or interferon. The median age of participants ranged from 53 to 69 years. The underlying malignancies were renal cell carcinoma, melanoma, non-small cell lung cancer, prostate cancer, hepatic cellular carcinoma, non-GIST sarcoma or neuroendocrine tumours.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

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

Data extraction
The number of patients with HFSR grade I or above, as defined by the National Cancer Institute Common Toxicity Criteria (definitions provided), and the total number of patients receiving sorafenib were extracted from each study. The proportion of patients with HFSR, along with 95% confidence intervals (CIs) were calculated. For controlled studies, the relative risk (RR) of HFSR among patients assigned to sorafenib compared against those assigned to the control group for that trial was also calculated. The authors stated neither how the data were extracted for the review nor how many reviewers performed the data extraction.

Methods of synthesis
The proportion of patients with HFSR was pooled using both fixed-effect and random-effects models. Heterogeneity was assessed using the Cochran Q statistic; where heterogeneity was significant only the results of the random-effects model were reported. Subgroup analysis was performed based on tumour type (renal cell carcinoma versus other types of malignancy). Relative risks from the included controlled studies were pooled using both fixed-effect and random-effects models.

Results of the review
Eleven trials were included in the review (n=4,883; range 22 to 2,502), including three randomised controlled trials (RCTs), two randomised discontinuation trials, five single arm phase II trials and one expanded access program trial.
Overall, the incidence of all-grade HFSR was 33.8 per cent (95% CI: 24.5, 44.7; n=3,797 evaluable patients). Incidence of grade III HFSR was 8.9 per cent (95% CI: 7.3, 10.7; n=4,020 evaluable patients).

Incidence of all-grade HFSR in patients with renal cell carcinoma was 42 per cent (95% CI: 24.9, 61.3; n=3252 evaluable patients). Incidence of all-grade HFSR in patients with non-renal cell carcinoma malignancies was 27.6 per cent (95% CI: 20.2, 36.4; n=545 evaluable patients).

The incidence of grade III HFSR in patients with renal cell carcinoma was 8.9 per cent (95% CI: 6.3, 12.3; n=3252 evaluable patients). The incidence of grade III HFSR in patients with non-renal cell carcinoma malignancies was 9.1 per cent (95% CI: 7.2, 11.3; n=545 evaluable patients).

All-grade HFSR was significantly more common in patients with renal cell carcinoma than those with non-renal cell carcinoma malignancies (RR 1.52, 95% CI: 1.32, 1.75, p<0.001), but there was no difference in the incidence of grade III HFSR.

The incidence of HFSR in patients receiving sorafenib was significantly greater than for those receiving placebo or interferon in the meta-analysis of the three RCTs (RR 6.6, 95% CI: 3.7, 11.7, p<0.001).

Authors' conclusions
Sorafenib was associated with a significant risk of developing HFSR in patients being treated for advanced solid tumours, particularly renal cell carcinoma.

CRD commentary
This review addressed a clear question supported by appropriate inclusion criteria. The authors searched electronic databases and manually searched conference abstracts, reducing the potential for publication bias. The authors did not state whether any language restrictions were applied and so the potential for language bias could not be assessed. The authors stated neither how studies were selected for the review nor how data extraction was performed, so the potential for reviewer bias and error could not be assessed.

The authors did not appear to have assessed the methodological quality of the included studies and insufficient study details were provided to allow the reader to assess the quality of the included studies. The sample sizes of the included studies varied greatly. Heterogeneity was assessed and the authors stated that the results of the random-effects meta-analyses would be reported in its presence. Although the results of the heterogeneity assessment were not reported, the results that were reported were from the random-effects meta-analyses, indicating that significant heterogeneity was present. Insufficient study details were presented to allow the reader to assess the clinical heterogeneity between studies. Subgroup analyses were performed to investigate the relationship between tumour type and the incidence of HFSR. Possible reasons for the difference in incidence for patients with different tumour types were discussed.

Although this review suffered from some limitations – such as poor reporting of some aspects of review methodology and a lack of quality assessment of the included studies – the overall conclusion reflected the results of the included studies and was likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that since sorafenib will be used more frequently in cancer patients, it was important that clinicians recognised the risk of patients being affected by HFSR and treat it properly as it may develop into a serious and devastating toxicity. They also advised that caution must be taken to monitor HFSR and other side effects when sorafenib was combined with other agents in clinical trials, owing to the unclear underlying mechanism.

Research: The authors stated that further research was necessary to investigate the pathogenesis and treatment of sorafenib-associated HFSR.

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