Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: a meta-analysis

Chu D, Lacouture ME, Weiner E, Wu S

CRD summary
This review concluded that sunitinib was associated with a significant risk of developing hand-foot skin reaction in patients with advanced cancer. The risk was greater in non-renal cell carcinoma malignancy. Methodological limitations mean that the review's estimates of incidence may not be accurate and that the conclusions based on these estimates may not be reliable.

Authors' objectives
To determine the risk of developing hand-foot skin reaction with sunitinib use.

Searching
PubMed was searched from January 1966 to July 2007 for relevant studies published in English. Search terms were reported. This search was supplemented by searches of Web of Science and abstracts from the 2004 to 2007 American Society of Clinical Oncology annual meetings.

Study selection
Prospective phase II and III trials that evaluated sunitinib as a single agent with intermittent or continuous daily dosing in cancer patients and that reported incidence of hand-foot skin reaction were eligible for inclusion.

Patients in included trials had renal cell carcinoma, gastrointestinal stroma tumour, urothelial cancer or gastric cancer. Most patients with renal cell carcinoma had received a nephrectomy. Control treatments included placebo and interferon-α (IFN-α). All patients who received sunitinib received 50mg once daily for four weeks then two weeks off (intermittent dosing) or 37.5mg daily (continuous daily dosing).

The authors did not state how many reviewers selected studies for inclusion.

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

Data extraction
Data were extracted on the proportion of patients with hand-foot skin reaction and 95% confidence intervals (CIs) were calculated for these proportions. Where a control arm was reported, relative risks (RRs) and associated 95% CIs were calculated.

The authors did not state how many reviewers performed the extraction.

Methods of synthesis
Incidence values were pooled using a fixed-effects model unless significant statistical heterogeneity was detected, in which case a random-effects model was used. Heterogeneity was investigated using Cochran's Q and $I^2$ statistics. Subgroup analyses were conducted by tumour type (renal cell carcinoma versus non-renal cell carcinoma) and dosing schedule (continuous versus intermittent).

Results of the review
Ten studies (n=5,005) were included in the review: two RCTs, two expanded-access trials and six single-arm phase II studies.

Incidence of all-grade hand-foot skin reaction (nine studies, n=4,436) was 18.9% (95% CI 14.1 to 24.8, $I^2=92$%).
Among patients with renal cell carcinoma (four studies, n=2,883) incidence was 14.4% (95% CI 8.0 to 24.6, \(I^2=92\%\)). Among patients with non-renal cell carcinoma (five studies, n=1,553) incidence was 23.3% (95% CI 16.2 to 32.3, \(I^2=87\%\)). There was a significant difference between these two subgroups (RR 0.56, 95% CI 0.50 to 0.64, \(p<0.001\)).

Incidence of high-grade hand-foot skin reaction (nine studies, n=4,281) was 5.5% (95% CI 3.9 to 7.9, \(I^2=77\%\)). Among patients with renal cell carcinoma (five studies, n=2,990) incidence was 4.7% (95% CI 2.8 to 7.8, \(I^2=72\%\)). Among patients with non-renal cell carcinoma (four studies, n=1,291) incidence was 7.8% (95% CI 6.5 to 9.4, \(I^2=26\%\)). There was a significant difference between the two subgroups (RR 0.60, 95% CI 0.47 to 0.77, \(p<0.001\)).

There was no significant difference in all-grade hand-foot skin reaction between intermittent and continuous sunitinib dosing schedules in non-renal cell carcinoma patients.

For the two randomised trials (n=1,039), sunitinib significantly increased potential development of hand-foot skin reaction compared with placebo/IFN-α (pooled RR 9.86, 95% CI 3.10 to 31.31).

**Authors' conclusions**
The authors concluded that sunitinib was associated with a significant risk of developing hand-foot skin reaction in patients with advanced cancer; the risk was greater in non-renal cell carcinoma malignancy.

**CRD commentary**
The review question was defined in terms of the participants, interventions, outcomes and study designs of interest. More than one source was used to identify potentially relevant literature, but including only English-language studies may have excluded relevant studies. No attempt was made to assess the quality of the included evidence. The authors did not state whether attempts were made to minimise potential for errors and bias in any of the review procedures. The authors used a random-effects model, but the extremely high levels of statistical heterogeneity for the main estimates of hand-foot skin reaction incidence may mean that the pooled values were not meaningful or accurate. The subsequent comparison of subgroups may be inaccurate, so the authors' conclusions based on these estimates cannot necessarily be considered reliable.

Review authors were supported by Robert H. Lurie Cancer Centre and Research Foundation of the State University of New York.

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

**Practice:** The authors stated that patients who received sunitinib should use supportive measures to avoid pressure points and extremes of temperature and friction, especially in the first month. Moisturising creams may be used for prevention and treatment of hand-foot skin reaction.

**Research:** The authors stated that the significant risk of hand-foot skin reaction in sunitinib-treated patients warranted further clinical studies.

**Bibliographic details**

**PubMedID**
19213662

**DOI**
10.3816/CGC.2009.n.002
Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Agents /adverse effects; Carcinoma, Renal Cell /drug therapy /pathology; Drug Eruptions /etiology; Foot Diseases /chemically induced; Hand Dermatoses /chemically induced; Humans; Incidence; Indoles /adverse effects; Kidney Neoplasms /drug therapy /pathology; Paresthesia /chemically induced; Protein Kinase Inhibitors /adverse effects; Pyrroles /adverse effects; Risk Factors

AccessionNumber
12009105335

Date bibliographic record published
16/09/2009

Date abstract record published
31/03/2010

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.