Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients.
Ives NJ, Stowe RL, Lorigan P, Wheale K

CRD summary
This review assessed the effects of biochemotherapy for treating metastatic melanoma as compared to chemotherapy. It concluded that biochemotherapy clearly improved response rates, but did not appear to translate into a survival benefit. Given several considerations, particularly the lack of validity assessment and heterogeneity, the authors' conclusions should be interpreted with caution.

Authors' objectives
To compare the effects of biochemotherapy with chemotherapy for treating metastatic melanoma.

Searching
The Cochrane Library, MEDLINE, EMBASE, LILACS and Web of Science were searched between 1966 and September 2006. Search terms were reported. General medical journals, cancer journals, and conference proceedings were manually scanned. References of retrieved articles and the Cochrane Skin Group Ongoing Trials Register were also searched.

Study selection
Randomised controlled trials (RCTs) that compared biochemotherapy (immunotherapy with interferon-alpha and/or interleukin-2) plus chemotherapy with chemotherapy alone, for the treatment of metastatic melanoma, were eligible for inclusion.

Primary outcomes included response rates (definitions for partial and complete response were reported in the review), response duration, overall or median survival, and toxicity. Secondary outcomes included toxicity, time to disease progression, quality of life, overall survival, and time to treatment failure. Toxicity was defined as grade three or worse haematologic toxicity (thrombocytopenia, neutropenia, or leukopenia).

Included trials used varying doses and regimens of dacarbazine, temozolomide, vindesine, aranoza, cisplatin, carmustine, tamoxifen and vinblastine, alone or in various combinations. The majority of chemotherapy trials plus interferon-alpha used single agent regimens (mainly dacarbazine), while all chemotherapy trials plus interferon-alpha and interleukin-2 used combined regimens (dacarbazine and cisplatin). Treatment durations varied.

The authors did not state how studies were selected for inclusion.

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

Data extraction
Two reviewers independently extracted the number of events reported by each treatment group for dichotomous outcomes (response rates, progression-free survival, overall survival, and toxicity), ultimately to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Mean differences between outcome measure means for each treatment group were calculated, along with their variance for continuous variables (duration of response). Any discrepancies were resolved by consensus, or through referral to a third reviewer.

Methods of synthesis
The Mantel-Haenszel method was used to pool odd ratios for response rates and toxicity. Previously published methods were used to calculate survival end points. Mean difference for continuous variables were pooled to calculate the overall weighted mean difference with standard errors and 95% confidence intervals. Subgroup analysis was conducted by type of immunotherapy (interferon-alpha or interferon-alpha plus interleukin-2). Sensitivity analysis was performed by
removing the most heterogeneous trials.

The authors used the $\chi^2$ test to assess heterogeneity.

**Results of the review**

Eighteen RCTs (n=2,621 patients randomised, n=2,557 patients analysed) were included in the review. Analysed sample sizes ranged between 18 and 405 participants. Median follow-up durations ranged from 6.3 to 52 months, where reported.

**Response rates** (18 trial arms): There was a significant improvement in overall response rates using biochemotherapy compared to chemotherapy, OR 0.59 (95% CI: 0.49 to 0.72). However, there were no differences in overall response rates between the two biochemotherapy regimens using indirect comparison. There was no evidence of statistical heterogeneity among trials. Partial and complete response rates (and responses for both immunological subgroups) were significantly improved.

**Survival** (15 trial arms): Treatment with biochemotherapy showed no benefit in mortality rates compared to chemotherapy. There was evidence of heterogeneity ($X^2 = 0.006$), but this was no longer significant when the most heterogeneous trials were removed.

**Toxicity** (11 trial arms): A greater number of patients receiving biochemotherapy experienced thrombocytopenia (OR 3.03, 95% CI: 2.16 to 4.25) and neutropenia/leukopenia (OR 1.71, 95% CI: 1.25 to 2.34). There was evidence of significant heterogeneity between trials.

There were no statistical differences in treatment related deaths between the two treatment groups (12 trials) [A: 9 trials].

Duration of response and progression-free survival were also reported in the review.

**Authors’ conclusions**

Biochemotherapy clearly improved response rates in the treatment of metastatic melanoma, but this did not appear to translate into a survival benefit.

**CRD commentary**

The review objective was clear and was supported by appropriate inclusion criteria for participants, interventions, and study design. A comprehensive literature search was conducted using electronic databases and other appropriate sources, including a search for ongoing trials. The authors did not assess validity and reviewer error and bias cannot be ruled out for study selection. [A: The quality of all potential studies are assessed internally (usually independently by two systematic reviewers and/or statisticians), so reviewer bias is unlikely.] Appropriate methods were used to synthesise the data and investigate heterogeneity. However, analysis was somewhat limited as a number of trials did not provide sufficient data to allow analysis, and there was significant heterogeneity between trials for some outcome measures. Also, confidence intervals were wide for some trials, which reduced the reliability of the results. There were considerable differences in treatment regimens between trials, and as there was little data provided on patient characteristics, such as age and disease progression, it was unclear whether the patients were comparable. Given the above considerations, in particular the lack of validity assessment and heterogeneity, the authors’ conclusions should be interpreted with caution as they may not be reliable.

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

**Practice:** The authors stated that in certain clinical settings increased response rates may be useful outcomes, but this needs to be considered along with any increase in toxicity associated with this approach.

**Research:** The authors did not state any implications for future research.

**Funding**

---

Database of Abstracts of Reviews of Effects (DARE)
Produced by the Centre for Reviews and Dissemination
Copyright © 2020 University of York
The review was not supported by any specific grant funding, but three authors were supported through a core grant from the National Co-ordinating Centre for Research Capacity Development.

Bibliographic details

PubMedID
18048825

DOI
10.1200/JCO.2007.12.0253

Original Paper URL
http://jco.ascopubs.org/cgi/content/abstract/25/34/5426

Additional Data URL
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005413/frame.html

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Agents /administration & dosage /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Humans; Interferon-alpha /administration & dosage; Interleukin-2 /administration & dosage; Melanoma /drug therapy /pathology; Randomized Controlled Trials as Topic

AccessionNumber
12008009046

Date bibliographic record published
03/11/2008

Date abstract record published
07/10/2009

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.