Single-agent DTIC versus combination chemotherapy with or without immunotherapy in metastatic melanoma: a meta-analysis of 3273 patients from 20 randomized trials

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Authors' objectives
To compare the response rates of single-agent dacarbazine (DTIC) for metastatic melanoma to combination chemotherapy with or without immunotherapy.

Searching
MEDLARS (from 1970 to 1999), Cancerlit, EMBASE and Current Contents were searched. The bibliographies of studies were searched manually and relevant textbooks were reviewed. Studies reported in any language were applied, and both abstracts and full publications were eligible. Review articles and letters were excluded.

Study selection

Specific interventions included in the review
Only studies of single-agent DTIC were eligible. The comparator interventions could include any chemotherapy combinations (including DTIC-containing regimens) or chemotherapy with or without immunotherapy. Endocrine interventions, in the form of tamoxifen, were also eligible.

The DTIC regimens varied. Most of the regimens in the control arms were DTIC (range: 2.5 to 800 mg/m2) for 4 or 5 days every 3 to 4 weeks; other regimens included DTIC given in a single course. DTIC-containing regimens in the study arms included DTIC plus the following, either alone or in combination: interferon-alpha, cisplatin, vinblastine, lomustine, carmustine, hydroxyurea, cornebacterium parvum, detorubicin, tamoxifen, methyl-CCNU, epirubicin, vindesine, and bacillus Calmette-Guerin vaccine. Non-DTIC-containing regimens in the study arms included combinations of nitrosomethylurea, dactinomycin, carmustine, vincristine, vinblastine, bleomycin, and cisplatin.

Participants included in the review
Adults with stage IV (metastatic) cutaneous malignant melanoma were eligible. Studies that included patients with anything other than stage IV disease were excluded unless they were stratified by stage of the disease.

Outcomes assessed in the review
The question addressed in the review referred to tumour response and overall survival, although the inclusion criteria were not specifically defined in terms of the outcomes. The primary outcome was the tumour response ratio (complete or partial). Other outcomes were time to tumour progression and overall survival.

How were decisions on the relevance of primary studies made?
One investigator screened the initial citations; selected citations were then screened for eligibility according to the inclusion criteria. The authors do not state how many of the reviewers performed the selection.

Assessment of study quality
The included studies were restricted to RCTs but no validity assessment was undertaken. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The authors do not state how many of the reviewers performed the data extraction.
The following data were extracted onto a data extraction form: year of publication; details of the intervention regimen; prior chemotherapy; the number of patients randomised and the number analysed; the percentage of female patients; prior chemotherapy; mean or median Karnofsky or other measures of performance status; percentage with visceral metastases; the presence or absence of brain metastases; the number of metastatic sites; response rate (complete plus partial); the median time to tumour progression; and overall survival. In cases of multiple publications, data were extracted from the most recent report.

**Methods of synthesis**

How were the studies combined?

The pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using the fixed-effect model described by Yusuf et al. (see Other Publications of Related Interest no.1). DTIC as a single agent was compared with DTIC plus immunotherapy (interferon), DTIC-containing regimens, and non-DTIC-containing regimens.

How were differences between studies investigated?

Statistical homogeneity was assessed using the Q statistic prior to estimating the pooled OR. Sensitivity analyses were performed in cases of heterogeneity.

**Results of the review**

Twenty RCTs (3,273 patients randomised) were included.

Of the patients randomised, 83% were included in the analyses.

The overall survival for patients treated with DTIC as a single agent was 7.4 (plus or minus 0.6) months. The response rates for the various regimens were as follows: 16.9% (95% CI: 14.7, 19.1) for DTIC alone; 21.5% for DTIC plus immunotherapy (interferon); DTIC-containing regimens, and non-DTIC-containing regimens.

DTIC versus all other combination drug regimens. Regimens with single-agent DTIC were associated with significantly poorer tumour response rates than combination therapy. The OR was 1.23 (95% CI: 1.02, 1.48). There was no evidence of heterogeneity (Q = 23.6, d.f.=26).

DTIC versus non-DTIC containing regimens (4 RCTs).

There was no statistically-significant difference in the response rates between the interventions. The OR was 0.77 (95% CI: 0.45, 1.32).

DTIC versus DTIC-containing regimens (10 RCTs, 1,273 patients).

There was a marginally non statistically-significant difference in the response rates between the interventions. The OR was 1.33 (95% CI: 0.99, 1.78).

DTIC versus DTIC plus interferon. Regimens using a combination of DTIC and interferon were associated with significantly greater response rates than DTIC alone. The OR was 1.53 (95% CI: 1.10, 2.13, p=0.01). Survival curves were available for five DTIC plus interferon treatment arms, and these showed no statistically-significant difference between single-agent DTIC regimens and combination therapy regimens. The OR was 1.16 (95% CI: 0.87, 1.54).

**Authors’ conclusions**

The combination of DTIC plus interferon appeared more active than standard single-agent DTIC in metastatic melanoma.

**CRD commentary**

The aims were stated and the inclusion criteria were defined in terms of the participants, study design and intervention. Several relevant databases were searched and no language restrictions were applied. The authors provided limited
information on their methodology with no detail of any independent checking of the study selection process. The included studies were restricted to RCTs but no formal validity assessment was undertaken. Some relevant data were tabulated. The data were pooled in a meta-analysis and statistical heterogeneity was assessed. The authors considered some of the limitations of the review in the text.

The authors acknowledged the absence of an assessment of quality of life. The evidence presented supports the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors state that the response rates were greater for the combination of DTIC plus interferon when compared with standard single-agent DTIC.

Research: The authors state that further RCTs of DTIC plus interferon are required to confirm the results of the review. The authors also state that future clinical trials must control for recognised prognostic factors, and also assess changes in the patients’ functional status and quality of life in addition to clinical response.

Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
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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.