Treatments for metastatic melanoma: synthesis of evidence from randomized trials

CRD summary
The authors concluded that outcomes were generally poor with dacarbazine treatment for metastatic melanoma. They also found that the addition of other therapies offered minimal clinical advantages and that included trials were generally small and of poor quality. These findings are likely to be reliable but should be interpreted with some caution due to lack of details on data synthesis.

Authors’ objectives
To determine the efficacy and safety of dacarbazine alone and in combination for the treatment of non-resectable metastatic melanoma.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Library were searched from inception to 2006. Search terms were reported. Reference lists of relevant articles were screened. No language restrictions were applied. Only studies published in peer reviewed journals were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) that compared dacarbazine, alone or in combination, with other treatments, standard care or placebo, in adults with non-resectable Stage III or IV cutaneous malignant melanoma, were eligible for inclusion. Other treatments could include a systemic chemotherapy (e.g. biologic response modifier such as interferon or interleukin), immunostimulating therapy or combinations of other agents. Melanoma stage had to be identified according to the system of the American Joint Committee on Cancer. Trials that assessed local therapies, such as surgery or radiation, were excluded unless data could be extracted separately for the non-local therapy arms. Outcomes of interest were success rate (objective response rate, which was the sum of complete and partial response), median survival and adverse events.

All of the included trials compared dacarbazine alone or in combination to the following active treatments: standard chemotherapies such as alkylating agents (carmustine, cyclophosphamide, fotemustine, lomustine, piperazinedione, procarbazine, semustine and temozolomide); antineoplastic antibiotics (bleomycin, dactinomycin, doxorubicin, doxorubicin and epirubicin); vinca alkaloids (vinblastine, vincristine and vindesine); platinum compounds (cisplatin and carboplatin); tamoxifen; ICRF, the topoisomerase II-targeting drug; ureas (hydroxyurea and nitrosomethylurea); biologic response modifiers; and/or immunostimulating therapy (Bacille Calmette-Guerin (BCG) vaccine, interferons, interleukins, Corynebacterium parvum preparation). In included trials, the mean age of participants ranged from 45 to 64 years and the proportion of men ranged from 43 to 73%, where reported.

Studies were assessed for relevance independently by two reviewers.

Assessment of study quality
Trials were assessed for methodological quality against the criteria of: mode of randomisation, blinding and mode of blinding, sample-size calculation and numbers of participants lost to follow-up or withdrawn. No overall quality score was used.

Data extraction
Data were extracted on: median duration of survival; complete and partial responses, stable and progressive diseases; and grade 3 and 4 side effects (nausea, vomiting, neutropenia, anaemia, thrombocytopenia, febrile neutropenia and any other clinically important side effects). Treatment responses and toxicity were classified according to World Health Organisation criteria. Data were extracted on an intention-to-treat basis where possible. If appropriate data were not reported, data were extracted on number of evaluable patients. Data were extracted as odds ratios together with their 95% confidence intervals.

Two reviewers independently extracted data using a standardised form. Discrepancies were resolved through consensus.
or referral to a third reviewer where necessary.

**Methods of synthesis**
A random effects-model was used to combine odds ratios from trials that compared dacarbazine monotherapy to all other treatments. Heterogeneity was assessed using the $\chi^2$ and $I^2$ statistics. Sensitivity analyses were conducted to exclude trials thought to be responsible for any observed heterogeneity.

**Results of the review**
Forty eight randomised controlled trials (RCTs) were included (7,135 patients). Trial quality was generally poor. Only 11 trials reported appropriate methods of randomisation. Two trials appropriately described blinding. Nineteen trials reported sample size calculations. Less than 60% of trials provided details on number of patients lost to follow-up.

**Dacarbazine monotherapy** (23 RCTs, 3,356 patients): Success rate was greater with dacarbazine monotherapy than all other treatments (odds ratio 1.31, 95% confidence interval (CI): 1.06 to 1.61). There was no evidence of statistical heterogeneity ($I^2=10.7\%$, $p=0.32$). There was no difference between dacarbazine monotherapy and non-dacarbazine therapies (odds ratio 1.10, 95% CI: 0.74 to 1.63; based on seven RCTs). Adjunct therapy (co-administration of dacarbazine plus an additional drug) was more effective than dacarbazine alone (OR=1.40, 95% CI: 1.10, 1.79; based on 16 RCTs). In particular, dacarbazine plus interferons was significantly more effective than dacarbazine alone (odds ratio 1.69, 95% CI: 1.07 to 2.68; based on six RCTs). Median duration of survival did not differ between treatment groups (Mann-Whitney test, $z=1.18$, $p=0.24$).

**Dacarbazine combination therapy** (25 RCTs, 3,779 patients): None of the individual trials reported significant differences in response between dacarbazine combination therapy and other treatments. Dacarbazine combined with interferons was found to be more effective than similar regimens without interferons (odds ratio 1.57, 95% CI: 1.15 to 2.15, number of RCTs unclear), but median survival times did not differ (Mann-Whitney test, $Z=1.06$, $p=0.92$). There were no additional benefits of interleukins when added to regimens including interferons (OR=0.83, 95% CI: 0.58 to 1.19; based on three RCTs).

**Adverse events:** All but two trials reported adverse events but only half of these were extractable using World Health Organization standardised toxicity data. Dacarbazine was generally well tolerated. Major adverse effects were limited to nausea and vomiting. Myelosuppression, alopecia and fatigue were minimal. The greater the number of agents included in the treatment regimen, the greater the number and severity of adverse events.

**Authors’ conclusions**
Outcomes were generally poor with dacarbazine treatment. The additional of other therapies offered minimal clinical advantages, although some, like interferons, may warrant further investigation. Trials were generally small and of poor quality.

**CRD commentary**
The review addressed a focused question, supported by defined inclusion criteria. The literature search was adequate but the review was restricted to published studies, so there is a possibility of publication bias. Appropriate steps were taken to minimise bias and errors in the selection of studies and extraction of data, but it was unclear whether such steps were also taken to the assessment of study quality. The quality assessment considered some appropriate criteria but consideration of other potential biases, such as concealment of treatment allocation, would have been preferable. Trial details were adequately presented in tables, but further details on the study participants would have helped determine the generalisability of results. The methods used to pool response rate data appeared appropriate, but detail was lacking on the treatment of survival data, for example, how duration of survival was compared between groups was not reported. The authors’ conclusions are likely to be reliable but should be interpreted with some degree of caution due to the limited reporting of synthesis methods.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that future studies should improve standardised reporting of adverse effects and be directed at novel agents and prevention strategies.
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