Tamoxifen vs non-tamoxifen treatment for advanced melanoma: a meta-analysis

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CRD summary
This generally well-conducted review concluded that chemotherapy with tamoxifen improved overall response and partial response in patients with advanced melanoma compared with chemotherapy without tamoxifen, but that it did not reduce mortality at one year. However, the poor quality of included data limits the reliability of the pooled results.

Authors’ objectives
To assess the benefits and harms of systemic therapy plus tamoxifen compared with systemic therapy without in patients with advanced melanoma (skin cancer).

Searching
EMBASE, PubMed, LILACS, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to February 2009 for articles published in any language. Search terms were reported. Reference lists of identified articles were handsearched. Conference proceedings and trial registers were scanned. Field experts and pharmaceutical companies were contacted for unpublished and ongoing trials.

Study selection
Randomised controlled trials (RCTs) that compared chemotherapy with or without the use of tamoxifen in patients with a confirmed diagnosis of advanced melanoma (grade III/IV of the American Joint Committee on Cancer) were eligible for inclusion.

Primary outcomes were overall response, complete response, partial response and mortality. Secondary outcomes were toxicity, treatment-related mortality, and quality of life (definitions provided in review).

Most included trials studied tamoxifen at a dose of 20mg/day; some trials used 160mg/day dose. The comparator was predominantly other chemotherapy, although placebo was also used. The mean age of included patients ranged from 46.8 to 55 years; the male-female ratio ranged from 0.6 to 2.3. Intention-to-treat data were used in some trials.

Two reviewers performed study selection and disagreements were resolved by discussion.

Assessment of study quality
Two authors independently evaluated trial validity using the Cochrane Collaboration Guidelines, which assessed randomisation, blinding, allocation concealment, intention-to-treat analysis, completeness of follow-up, selective outcome reporting, and definitions of interventions and outcomes. Disagreements between reviewers were resolved by discussion.

Data extraction
Data were extracted on overall response, complete response, partial response, mortality and toxicity. The data were used to calculate relative risks (RRs) together with 95% confidence intervals (CIs). Trial authors were contacted for missing data. When intention-to-treat was not conducted, data were treated as missing data and data imputation was employed. Data were re-checked for errors during data entry.

Methods of synthesis
A random-effects meta-analysis was undertaken to calculate pooled relative risks and 95% confidence intervals. Heterogeneity was assessed using X^2 and I^2. Subgroup analyses were undertaken based on funding source, gender, and tamoxifen dose.

Publication bias was assessed using funnel plots.

Results of the review
Nine RCTs were included in the review (n=1,290 patients). The trial sample size ranged from 42 to 271 patients.
Length of follow-up ranged from 20 to 156 months. The quality of the included trials was generally poor, with few trials adequately concealing allocation, performing blinding, or randomising patients to treatment groups. The maximum loss to follow-up was 11%.

**Efficacy**: Compared with control chemotherapy, chemotherapy plus tamoxifen was associated with a statistically significant greater effect in overall response (RR 1.36, 95% CI 1.04 to 1.77; I² = 23%; nine trials) and partial response (RR 1.69, 95% CI 1.29 to 2.22; I² = 0%; nine trials), but there was no statistically significant difference in complete response. There was no statistically significant difference in mortality at one year or at two years. No trials reported on quality of life.

**Adverse events**: There were no statistically significant differences in haematological toxicity, non-haematological toxicity, or treatment related mortality between chemotherapy with tamoxifen versus chemotherapy without tamoxifen (control).

Subgroup analysis revealed that there was a trend towards a greater overall response in trials with a higher female-male ratio.

There was some evidence of asymmetry in funnel plots, which indicated potential publication bias.

**Authors' conclusions**
Chemotherapy with tamoxifen improved overall response and partial response, but did not improve one-year mortality in patients with advanced melanoma compared with chemotherapy without tamoxifen.

**CRD commentary**
Inclusion criteria for the review were clearly defined. Several relevant data sources were searched without language restrictions. Publication bias was assessed; the authors reported there was potential bias. Attempts were made to reduce reviewer error and bias throughout the review.

Quality assessment was undertaken using a standard tool, which indicated the included trials were of generally poor quality. Trials were pooled using random-effects meta-analysis; statistical heterogeneity was assessed, which was appropriate. The authors appropriately acknowledged that the applicability of results to practice was limited and that more information was needed.

Overall, the review was generally well conducted, but the poor quality of data limits the reliability of the pooled results.

**Implications of the review for practice and research**
**Practice**: The authors stated that further use of tamoxifen in patients with melanoma should only be considered in the context of clinical trials.

**Research**: The authors stated that further high-quality research is needed, particularly to assess the effects in women compared with men. Trials should have a clear division of cancer stages. More information on the harms of tamoxifen, and research to assess quality of life is also needed.

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