The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumours: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that melatonin as an adjuvant therapy for solid tumour cancer led to substantial improvements in tumour remission, one-year survival, and alleviation of radiochemotherapy-related side effects. Although the results were based mainly on small single-centre studies, the authors’ conclusion reflects the moderate-quality evidence presented and seems likely to be reliable.

Authors' objectives
To evaluate the efficacy and safety of melatonin as adjuvant therapy for patients with solid tumour cancer.

Searching
PubMed, EMBASE, The Cochrane Library, and CNKI (China National Knowledge Infrastructure) were searched from inception to November 2011. Search terms were reported. References of relevant articles were screened. The related-articles function within PubMed was used to identify further studies.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) of melatonin as adjuvant treatment to chemotherapy or radiotherapy in patients with pathologically-confirmed malignancy. Trials had to report on tumour remission, one-year survival, or chemoradiotherapy-related side effects. Trials that compared melatonin in combination with other anticancer agents apart from standard chemotherapy were excluded.

Most included trials were conducted in Italy from 1996 to 2007; all were funded by hospitals. The mean age of included patients ranged from 50 to 65 years. Most patients had metastatic solid malignancy of the lung, breast, liver, gastrointestinal tract, head, and neck. Some trials focused only on metastatic non-small cell lung cancer. Most trials compared chemotherapy plus melatonin versus chemotherapy alone. The melatonin dose was 20mg orally, once daily.

Two reviewers independently selected the trials for inclusion.

Assessment of study quality
Trial quality was assessed on the following criteria: method of randomisation, allocation concealment, blinding of patients and assessors, use of placebo, and loss to follow-up.

The authors did not state how many reviewers assessed the quality of included trials.

Data extraction
Data were extracted to enable the calculation of relative risks (RR) and 95% confidence intervals (CI). Authors were contacted for missing data, where necessary.

This process was carried out independently by two reviewers and disagreements were resolved by discussion.

Methods of synthesis
A random-effects meta-analysis was conducted, focusing on the efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy. Statistical heterogeneity was assessed using $X^2$ and $I^2$.

Results of the review
Eight RCTs (768 participants, sample size range 30 to 250) were included in the meta-analysis. Overall trial quality was considered to be moderate. One trial reported the method of randomisation. All trials reported allocation concealment. Blinding or use of placebo were not present in any of the trials. Loss to follow-up was unknown in most trials.

Melatonin therapy was associated with significantly increased complete or partial tumour remission (RR 1.95, 95% CI
1.49 to 2.54; eight trials; I²=0%), and survival at one year (RR 1.90, 95% CI 1.28 to 2.83; five trials; I²=61.9% indicating significant heterogeneity).

Melatonin therapy was associated with significantly fewer side effects for thrombocytopenia (RR 0.13, 95% CI 0.06 to 0.28; five trials; I²=0%), neurotoxicity (RR 0.19, 95% CI 0.09 to 0.40; five trials; I²=0%), and fatigue (RR 0.37, 95% CI 0.28 to 0.48; five trials; I²=0%).

Authors’ conclusions
Melatonin as an adjuvant therapy for cancer led to substantial improvements in tumour remission, one-year survival, and alleviation of radiochemotherapy-related side effects.

CRD commentary
The review question was clear. The inclusion criteria were specified in detail. A selection of relevant data sources was searched. There was no apparent search for unpublished trials or reported assessment of publication bias. This meant that relevant trials might have been missed. The processes of study selection and data extraction were carried out with steps to minimise error and bias.

Relevant quality assessment criteria were applied to the included trials; the results of this assessment were clearly reported. Trial details were provided. Statistical heterogeneity was assessed. The chosen method of synthesis seemed appropriate. The authors acknowledged limitations of the review in the reliance of a small number of single-centre studies.

The authors’ conclusion reflects the moderate-quality evidence presented and seems likely to be reliable.

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

Research: The authors stated that international multi-centre RCTS with larger sample sizes were needed to confirm the efficacy and safety of melatonin as an adjuvant therapy in patients with cancer.

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