Impact of antioxidant supplementation on chemotherapeutic efficacy: a systematic review of the evidence from randomized controlled trials


CRD summary
This well-conducted review assessed concurrent antioxidant supplementation in chemotherapy for cancer patients. The authors concluded that there was no evidence of a detriment to chemotherapy efficacy. Indications of improved outcomes were found with supplementation, but further adequately powered trials were required. These cautious conclusions are likely to be reliable.

Authors' objectives
To assess the effect of concurrent use of antioxidants with chemotherapy.

Searching
MEDLINE, CINAHL, AMED/AltHealthWatch, EMBASE, and CENTRAL were searched from inception to December 2006. Search terms are available from the authors. No language restrictions were employed. References of key articles and reviews were checked.

Study selection
Randomised controlled trials (RCTs) of oral or intravenous antioxidants in cancer patients undergoing current chemotherapy were eligible for inclusion in the review. Studies of whole herbs and multicomponent herbal formulas containing phytochemical antioxidants were excluded from the review. The primary review outcomes were survival and tumour response.

Included studies assessed the antioxidants: glutathione, melatonin, vitamin A, vitamin C, N-Acetylcysteine, vitamin E, ellagic acid and mixed interventions. All studies used placebo comparators. A wide range of chemotherapeutic regimes were used. Principal agents included oxaliplatin, cisplatin combined with etoposide and fluorouracil, mitomycin, gemcitabine, doxorubicin, paclitaxel, mitoxantrone, vinorelbine, busulfan, cyclophosphamide combined with methotrexate and fluorouracil, and CPT-11. A number of types of cancer were represented, most commonly including breast, lung and gastric cancers. Most patients had relapsed or advanced cancer. Neurotoxicity and chemotherapy completion were assessed as secondary outcomes.

Two reviewers independently assessed the studies for inclusion.

Assessment of study quality
Two reviewers independently assessed the studies for validity using the Jadad scale, which produces a composite score of 0 to 5 points. Where necessary, authors were contacted for verification of randomisation.

Data extraction
Two reviewers performed the data extraction. The statistical significance of between-group differences in outcomes was calculated.

Methods of synthesis
The studies were combined in a narrative synthesis grouped by the antioxidant(s) employed.

Results of the review
Nineteen RCTs (n = 1,554) were included in the review. Jadad scores ranged from 1 to 5, with five trials scoring 3 or higher. Sample size ranged from 20 to 250, 11 RCTs included 60 or fewer patients.

Glutathione (seven RCTs): two of six RCTs found statistically significantly lower levels of neurotoxicity in the interventions groups (p = 0.0001 and p = 0.01). The direction of effect was the same in the studies showing non-
significant results. One RCT found significantly higher chemotherapy completion rates in the intervention group (58 per cent versus 39 per cent, \( p = 0.04 \)), with a significantly lower rate of non-completion due to nephrotoxicity (\( p = 0.012 \)). There were no significant differences in survival or response rate, although one subgroup analysis in one RCT showed an increased complete response rate (\( p = 0.014 \)).

Melatonin (four RCTs): three RCTs reported statistically significant improved survival either at one year (two RCTs, \( p < 0.05 \) and \( p < 0.001 \)) or five years (one RCT, \( p < 0.001 \)) in the intervention groups. The final study reported a significantly higher rate of disease stabilisation in the melatonin group (\( p < 0.05 \)).

Mixed interventions (two RCTs): one RCT evaluated vitamins C and E with beta carotene and the other assessed vitamins C and E with selenium. No significant differences between the groups were observed.

Vitamin E (one RCT): there was a significantly lower rate of neurotoxicity in the supplement group (31 per cent versus 86 per cent, \( p < 0.01 \)). There was no significant difference in tumour response between the groups.

Ellagic acid (one RCT): there was a significantly lower rate of neutropenia in the supplement group (33 per cent versus 75 per cent, \( p < 0.05 \)). There was no significant difference in complete response rate or two-year survival rate between the groups.

Vitamin A (two RCTs): one RCT found a higher rate of complete response in the supplement group (38 per cent versus 15 per cent, \( P < 0.02 \)) and a higher projected 43-month survival rate (93 per cent versus 30 per cent, \( p < 0.02 \)) and these outcomes also showed significant differences for a postmenopausal subgroup; the second RCT found no significant differences in efficacy outcomes, but a lower rate of grade 2 or higher toxicities in the supplement group (4 per cent versus 23 per cent, \( p = 0.002 \)).

No significant differences between the groups were observed for N-acetylcysteine (one RCT) or vitamin C (one RCT).

Authors' conclusions
There was no evidence of significant decreases in the efficacy of chemotherapy with antioxidant supplementation. There were some indications of improvements in survival, tumour response and incidence of toxicity, but studies were underpowered. Large well-designed studies of concurrent antioxidant supplementation in chemotherapy are required.

CRD commentary
The review question and the inclusion criteria were clear if broad. The authors searched a number of databases without language restrictions, although they did not report searching systematically for unpublished studies. This may have increased the chances of relevant articles being excluded and publication bias. The authors reported using rigorous methodology at all stages of the review process, reducing the chances of error and bias. An appropriate validity assessment was conducted. In view of the level of clinical heterogeneity between included studies, the decision to employ a narrative synthesis was clearly appropriate. This was a generally well-conducted review and the authors' cautious conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: the authors stated that further exploration of the clinical application of antioxidant supplementation was warranted.
Research: the authors stated that large well-designed studies of concurrent antioxidant supplementation in chemotherapy were required.

Funding
Not stated.

Bibliographic details
Database of Abstracts of Reviews of Effects (DARE)  
Produced by the Centre for Reviews and Dissemination  
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