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MINI REVIEW

Impact of antioxidant supplementation on chemotherapeutic toxicity: A systematic review of the evidence from randomized controlled trials

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Much debate has focused on whether antioxidants interfere with the efficacy of cancer chemotherapy. The objective of this study is to systematically review the randomized, controlled clinical trial evidence evaluating the effects of concurrent use of antioxidants with chemotherapy on toxic side effects. We performed a search of literature from 1966-October 2007 using MEDLINE, Cochrane, CinAhl, AMED, AltHealthWatch and EMBASE databases. Randomized, controlled clinical trials reporting antioxidant-based mitigation of chemotherapy toxicity were included in the final tally. Searches were performed following a standardized protocol for systematic reviews. Only 33 of 965 articles considered, including 2,446 subjects, met the inclusion criteria. Antioxidants evaluated were: glutathione (11), melatonin (7), vitamin A (1), an antioxidant mixture (2), *N*-acetylcysteine (2), vitamin E (5), selenium (2), L-carnitine (1), Co-Q10 (1) and ellagic acid (1). The majority (24) of the 33 studies included reported evidence of decreased toxicities from the concurrent use of antioxidants with chemotherapy. Nine studies reported no difference in toxicities between the 2 groups. Only 1 study (vitamin A) reported a significant increase in toxicity in the antioxidant group. Five studies reported the antioxidant group completed more full doses of chemotherapy or had less-dose reduction than control groups. Statistical power and poor study quality were concerns with some studies. This review provides the first systematically reviewed evidence that antioxidant supplementation during chemotherapy holds potential for reducing dose-limiting toxicities. However, well-designed studies evaluating larger populations of patients given specific antioxidants defined by dose and schedule relative to chemotherapy are warranted.

Key words: alternative medicine; complementary medicine; cancer; chemotherapy; antioxidants

The published literature suggests that antioxidant supplements are taken by 13–87% of patients with cancer.[1–10] Such a wide range of percentages might result from the variability of definitions of complementary and alternative (CAM) medicine used in the different studies, and to differences in the cancer types, age, education, economic status, and ethnicity of the groups assessed.[11] Because cancer patients may take antioxidant supplements to help alleviate side effects from toxic chemotherapies, we systematically reviewed studies that evaluated the effects of antioxidants on chemotherapy-related toxicities. Much debate has focused on the use of antioxidant supplements by patients undergoing chemotherapy due to concerns that the antioxidants may interfere with the mechanism of action of the therapeutic agent and subsequently decrease its efficacy.[12] However, others argue that antioxidant supplements are beneficial to patients undergoing chemotherapy because they enhance the efficacy of the chemotherapy, as well as alleviate toxic side effects, allowing patients to tolerate chemotherapy for the full course of treatment and lessen the need for dose reduction.[13] We have previously reviewed randomized controlled trials in which antioxidants were given with chemotherapy and survival and tumor response outcomes were measured.[14] No indication was found that antioxidants were associated with decreased survival or tumor response, although further research with very large sample sizes would be required to definitively reject the hypothesis of interference. Our analysis suggested, in fact, that concurrent use of supplements and chemotherapy treatments might produce better tumor response rates and increased chances of survival, although small sample sizes and low quality of studies precluded firm conclusions.

A primary mechanism of many chemotherapy drugs against cancer cells is the formation of reactive oxygen species (ROS), or free radicals. Drugs that form ROS include but are not limited to alkylating agents (*e.g.*, melphalan, cyclophosphamide), anthracyclines (*e.g.*, doxorubicin, epirubicin), podophyllin derivatives (*e.g.*, etoposide), platinum coordination complexes (*e.g.*, cisplatin, carboplatin) and camptothecins (*e.g.*, topotecan, irinotecan). Unfortunately, these free radicals are often the source of serious side effects, as well. For example, nephrotoxicity, ototoxicity and peripheral neuropathy are often produced by cisplatin and other platinum-based chemotherapies.[15,16] Anthracyclines such as doxorubicin often cause cardiotoxicity.[17] Drugs such as the taxanes (*e.g.*, paclitaxel, docetaxel), vinca alkaloids (*e.g.*, vincristine, vinblastine), antimetabolites (*e.g.*, methotrexate, fluorouracil, cytarabine) generate lower levels of oxidative stress, and free radical damage is not considered their primary mechanism of action.[13,18] Asparaginase and dactinomycin are examples of chemotherapy drugs that use mechanisms other than oxidation for their anticancer effects. Clearly, interactions between chemotherapeutic compounds and antioxidants are complex and other factors affect the production of free radicals such as dose, localization and metabolism of the drug. In addition, some antioxidants have the potential to also act as oxidative molecules, depending on their use and/or relative concentration.

Of the supplements included in this review, antioxidant mechanisms range from free radical scavengers that act as reducers or that break lipid chains (melatonin, NAC, Vitamin E, GSH, beta carotene and vitamin C) to antioxidant enzymes formed by combining with a protein to form selenoproteins (selenium, GSH). Other mechanisms include metal chelators (Vitamin C, EGCG) or cellular protectors from free radical attack (vitamins A, C, E and melatonin) while some target and repair DNA aberrations (EGCG). Thus, understanding antioxidant-chemotherapy interactions is difficult enough in simple *in vitro* cell systems but exceedingly more difficult to define when using more complex animal tumor models. Further, the pharmacokinetics or pharmacodynamics of chemotherapy agents may be affected by certain antioxidants. These factors underline the need for an examination of the role of antioxidants in well-designed randomized clinical trials.

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Cancer patients often have low antioxidant levels prior to chemotherapy treatment,[19] and higher levels of oxidative stress have been linked with more aggressive cancers.[20–22] Therefore, administration of the aforementioned drugs exacerbates oxidative stress in cancer patients, as shown by DNA oxidation and lipid peroxidation levels during and after cancer therapy.[23,24] Theories suggest that antioxidant supplementation during the administration of these chemotherapies either hinders the cytotoxic mechanism(s) of chemotherapy by quenching ROS produced by the drug, or helps protect healthy cells from additional oxidative stress and toxicity from treatment. Clearly, the heart of the dilemma for patients with cancer lies in trying to understand whether antioxidant therapy will increase their quality of life through protection of normal tissues and possibly slow disease progression by lowering oxidative levels or interfere with the eventual clinical outcome of their disease.

Alternatively, patient outcomes may be improved by antioxidants through improving the therapeutic index of coadministered chemotherapy drugs, *i.e.*, increasing a patient's ability to tolerate full doses of antineoplastics with uninterrupted treatment schedules. The toxic side effects of chemotherapy often lead to dose reductions, interruptions and delays in chemotherapy treatment, and incomplete courses of treatment. A reduction in these side effects might result in an improved quality of life for the patient, and possibly better survival rates. In a recent study of colon cancer patients over age 65, those who received a full 5–7 months of chemotherapy had higher survival rates than those who only received 1–4 months of treatment. Furthermore, mortality rate among the 30% of patients who dropped out of chemotherapy treatment early was twice that of the group who completed therapy.[25] The reduction of toxic side effects from chemotherapy has clinical relevance, and many studies have evaluated the potential for antioxidants to contribute to this reduction. This review evaluates randomized, controlled trials in which studies measured side effects in patients given antioxidants concurrently with chemotherapy to determine if the antioxidants increased or decreased the side effects of the chemotherapy.

Material and methods

Electronic databases (MEDLINE, CENTRAL (The Cochrane Library), CinAhl, AMED/AltHealthWatch (combined) and EMBASE) were searched from inception through the last week of October, 2007. Database selection was based on inclusion of peer-reviewed alternative and complementary medicine articles. An identical search string was used in all databases with the exception of Medline which required the string to be altered to fit the database's particular terminology. Three categories were combined in attempts to cover as many variations as possible for (*i*) cancer (5), (*ii*) chemotherapy (24), and (*iii*) antioxidants (32). Authors will provide the detailed search string upon request. Searches were not restricted by language and were performed in duplicate (AK and MM). In the case of a disagreement, disputes were resolved through discussion among the authors until consensus was reached. Non-English abstracts were translated and if they appeared to meet inclusion criteria, the entire article was translated into English. Key articles and review papers were hand searched for additional references.

Searches yielded the following results: MEDLINE (368), AMED/AltHealthWatch (254), CENTRAL (284), CinAhl (90) and EMBASE (85). Abstracts were read as an initial screening. Full text was obtained for pertinent articles. In certain cases, further clarification or data was needed and authors were contacted. The resulting articles were screened for inclusion according to the criteria mentioned later.

Type of study

Only randomized, controlled trials that provided data on side effects were included in the review. Outcome data regarding side effects must be clinically-relevant and quantifiable according to the National Cancer Institute Common Toxicity Criteria or other standardized methods for assessing toxicities, *e.g.*, quality of life.

Study populations

Cancer patients who were currently undergoing only chemotherapy (not radiation) were included. All cancer types were included.

Type of therapy

Antioxidants were given (orally or intravenously) to patients concurrently with chemotherapy. Only trials administering chemotherapies that utilized ROS-producing mechanisms were included. [ROS-generating chemotherapy (doxorubicin, epirubicin, daunorubicin, idarubicin, cisplatin, carboplatin, oxaliplatin, bleomycin, carmustine, cyclophosphamide, melphalan, etoposide, mitomycin, vinblastine, vinorelbine, paclitaxel, docetaxel) together with an antioxidant compound (vitamin C, vitamin E, vitamin A, melatonin, glutathione, *N*-acetylcysteine, polyphenols, green tea catechins, carotenoids, carnitine, selenium, ellagic acid, curcumin, coenzyme Q10, lycopene, flavonoids, and isoflavones, including chemical names and synonyms of vitamin names]. Only antioxidant phytochemical extracts were included (not whole herbs or multicomponent herbal mixtures that contained phytochemical antioxidants) because of the potential for confounding of results by nonantioxidant activities of complex herbs and mixtures.

All data were obtained from published peer-reviewed reports for each trial. The Jadad scoring method was used by AK and CG to assess the quality of the included articles. This validated scale allows assessment of the methodological quality of each trial by analyzing the randomization, blinding methods, and description of patient dropouts/withdrawals of each study. This results in a score between 0 and 5, 0 indicating a weak study design and 5 indicating a strong study design.[26]

The screening and subsequent quality assessments of included articles were limited by what was available in the written report alone. Authors were contacted in certain cases for verification of randomization. The authors of this article have attempted to avoid publication bias by only including randomized, controlled trials that inherently reduce bias. However, the possibility of publication bias (preferential publication of positive trials) cannot be excluded.

Results

Of 965 references screened, 33 met the inclusion criteria, for a total of 2,446 patients evaluated. A flow chart shows the number of articles excluded for each factor (Fig. 1). Over half of the initial articles were excluded because they were not randomized, controlled trials (486). Many others were excluded because the antioxidant was not administered concurrently with chemotherapy (245). The remainder were excluded because the antioxidant was synthetic (44), the study included radiation (7), or the study was a preliminary report of an included study (6). Synthetic antioxidants have been included in previous reviews and therefore, were not included in this study.[27,28] All included papers were published in English; the papers in other languages were among the excluded classifications. The Jadad scoring method was used to evaluate all included studies. Jadad method and scores nearly spanned the entire range of quality from five to one. Jadad scores and the supplements reported in the trials are found in Tables I–IV.

The majority of the articles reported the use of glutathione (GSH) with chemotherapy (11) (see Table I). Melatonin (MLT) was dispensed in 7 of the studies, 6 of which were from the same group in Italy (see Table II). Five studies investigated vitamin E (see Table III). Two studies included selenium, two looked at a mix of antioxidants (vitamins C and E and selenium) and (vitamins C and E and beta-carotene) and two looked at *N*-acetylcysteine (see Table IV). Only 1 study was included for each of the

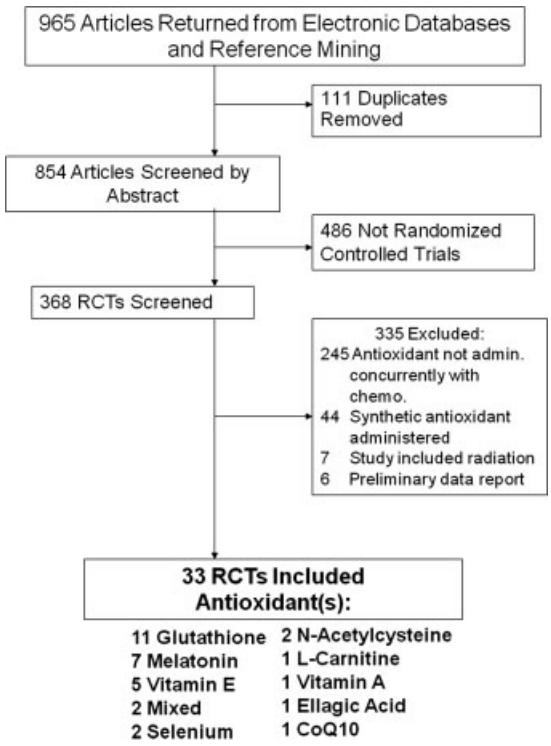

FIGURE 1 – Flow chart of exclusion process for systematic review.

following: vitamin A, ellagic acid, CoQ10 and L-carnitine (see Table IV).

Because the studies evaluated a variety of antioxidants in patients of several cancer types, meta-analysis was not considered advisable, and systematic review was chosen to summarize results of the studies.

Summary of studies

Glutathione (GSH). Of 9 GSH studies that evaluated neurotoxicity, 6 reported less neurotoxicity in the GSH group than the control group.[29,32–34,36,39] Four of these studies found the decrease to be statistically significant.[29,33,36,39] Myelosuppression was generally reported as similar between GSH and control groups with only 1 analysis where the control group experienced more anemia than the GSH group.[30] The remaining GSH studies reported similar general toxicities between the GSH and control groups. No GSH studies found a higher incidence of toxicities in the GSH group than the control group.

Melatonin (MLT). Seven studies reported a range of decreased toxicities from the antioxidant, many significantly, over control groups. Five studies, all from Lissoni *et al*., reported neurotoxicity was decreased in the MLT groups, with four of those statistically significant.[40,42–44,46] Myelosuppression was also consistently lowered in the MLT groups. Five studies, again by Lissoni *et al*., reported statistically significant decreases in myelosuppression.[40,42–44,46] Ghielmini *et al*. reported no difference between myelosuppression between the 2 groups.[45] All reports on cachexia (3)[40,43,46] asthenia (5)[40,42–44,46] stated a significantly significant decrease in the toxicities of the MLT group. The study by Cerea *et al*. found the MLT group experienced less grade 3–4 diarrhea requiring a 50% dose reduction than the control group.[41] Of note in the MLT studies is the increase in tumor response and survival times of the MLT groups over the control groups. However, the advanced disease stage of subjects in these trials, and the paucity of studies from research groups other than Lissoni *et al*. limit the generalizability of these results.

Vitamin E. Three studies reported significantly decreased neurotoxicity in the vitamin E group.[47,50,51] Another study reported significantly decreased oral mucositis the vitamin E group.[48] All other reports of toxicities found no significant differences in general toxicities between the 2 groups.[48–51]

Antioxidant mixture. Two studies reported on mixtures of antioxidant supplements. Both of these studies reported side effects to be similar between the antioxidant group and the control. Specifically, Pathak *et al*. reported alopecia, myelosuppression, diarrhea and neuropathy to be the same.[52] Weijl *et al*. evaluated nephrotoxicity and ototoxicity and found similar results between the 2 groups.[54]

Ellagic acid (EA). Falsaperla *et al*. investigated patients with hormone refractory prostate cancer and found no difference between the ellagic acid group and the control in terms of diarrhea, however, 33% of the antioxidant group versus 75% of the control experienced neutropenia ($p < 0.05$).[53]

Vitamin A. A study by Meyskens *et al*., found no difference between myelosuppression between the 2 groups. However, the study reported 23% of the vitamin A group experienced more grade 2+ toxicities versus 4% grade 2+ toxicities in the control group ($p = 0.002$).[56] This was the only statistically significant increase in toxicities in the antioxidant group of all the studies, although the vitamin A-specific toxicities were atypical of toxicities reported by other studies included in this review *i.e*., dry skin, personality changes, dry mouth, anxiety. While the control group experienced less Grade 2+ toxicity, they also had a significantly increased risk of disease progression and death compared to the vitamin A group.

N-acetylcysteine (NAC). Two studies evaluated NAC, however, one solely reported on the effect of the supplement on neuropathy. In a study by Lin *et al*., the NAC group experienced a marked decrease in neuropathy in comparison to the control group. Only 20% of the NAC group experienced grade 2+ neuropathy versus 89% in the control ($p < 0.001$).[57] In comparison, a study of NAC by Myers *et al*. found nonsignificantly increased toxicities in the NAC group over the control. These increased toxicities were alopecia and diarrhea, of 8 total toxicities measured. Other toxicities measured were similar between the 2 groups.[56]

L-carnitine. A study by Waldner *et al*. evaluated L-carnitine for potential protection against cardiotoxicity.[58] However, neither the L-carnitine or control group experienced cardiotoxicity.

Coenzyme Q10 (CoQ10). Iarussi *et al*. also evaluated the potential for an antioxidant, CoQ10, to protect from cardiotoxicity.[59] By evaluating the left ventricular fraction time of each group of patients, Iarussi determined the CoQ10 group had a lower ejection fraction than the control group and therefore was protected from cardiotoxicity.

Selenium (Se). Two studies of selenium found significant decreases in toxicities in the antioxidant groups. Sieja *et al*. found a statistically significant decrease in alopecia, myelosuppression and asthenia.[60] Federico *et al*. also reported a statistically significant decrease in asthenia in the selenium group versus the control.[61]

Conclusions

The majority of evidence from studies included in this review suggests that antioxidant supplementation may reduce the toxic effects of ROS-generating chemotherapies. Of a total of 86 separate reports on toxicities, 53% in (46) showed the antioxidant group experienced less toxicity than the control group. Of that 53, 82% of those studies reported a statistically significant difference in toxicity. About 43% in (37) of the reports stated no difference in toxicities between the antioxidant group and the control. About 4% of the reports showed an increase in toxicities in the antioxidant group over the control group. Only one of the reports of increased toxicities was statistically significant. This report stated the antioxidant group experienced more general toxicities of grade

TABLE I – RANDOMIZED CLINICAL TRIALS WITH GLUTATHIONE (GSH) AND CHEMOTHERAPY

Reference	Tumor type(s)	No. of pts	GSH protocol	Chemotherapy regimen	Toxicity mitigation in GSH group *vs.* Control group	Responses in GSH group *vs.* Control group	Conclusion	Jadad score
Cascinu *et al.*, 2002[29]	Advanced colorectal cancer	n = 52, 26 chemo + GSH, 26 chemo + placebo	1,500 mg/m^2 given IV over 15 min, immediately before chemo	Oxaliplatin 100 mg/m^2 as IV infusion, followed by 5FU, 1500 mg/m^2 as IV 24-hr infusion with leucovorin, 150 mg/m^2 as infusion	30% *vs.* 100% in GSH *vs.* control groups experienced grade 2-4 neurotoxicity (p = 0.004); incidence and severity of other toxicities were similar between the groups	CR + PR rates were 27% *vs.* 23% in GSH *vs.* control groups; neither group reported a CR; Median survival: 16 *vs.* 17 months	GSH group experienced significantly reduced neuropathy *vs.* control group	5
Schmidinger *et al.*, 2000[30]	Advanced NSCLC and HNC	n = 20, 6 with NSCLC, 14 HNC; 11 chemo + GSH, 9 chemo + placebo	5,000 mg/m^2 given IV over 15 min, immediately before chemo	CDDP 80 mg/m^2 as IV infusion. HNC pts received 450 mg/m^2 5FU by IV bolus, NSCLC received 120 mg/m^2 IV VP-16, with cycles every 4 wks	Significant decrease in hemoglobin (p = 0.04), platelet counts (p = .03), and white blood cell counts (p = 0.004) in placebo *vs.* GSH groups; neither group experienced neurotoxicity	CR + PR rates were 55% *vs.* 50%; CR rates were 9% and 0%; Median survival: 13.1 months *vs.* 10.5 months	GSH group had significantly reduced hematological toxicities *vs.* the control group	2
Smyth *et al.*, 1997[31]	Ovarian cancer (Stages I-IV)	n = 151, 74 chemo + GSH, 77 chemo + placebo	3,000 mg/m^2 given IV over 20 min, immediately before chemo	CDDP 100 mg/m^2 as IV infusion every 3 weeks for six courses	58% *vs.* 39% were able to receive 6 cycles of CDDP (p = 0.04); 39% *vs.* 49% experienced neurotoxicity (p = 0.22)	CR + PR rates were 73% *vs.* 62% (p = 0.25); CR rates were 46% *vs.* 9%; survival rates were similar (stated in article)	GSH group had improved QoL scores, weight gain, neuroprotection, and nephroprotection and nonsignificantly higher tumor response rates *vs.* the control group	5
Bogliun *et al.*, 1996[32]	Advanced ovarian cancer	n = 54, 27 chemo + GSH, 27 chemo alone	2,500 mg/m^2 given IV over 15 min, immediately before chemo	CDDP 50 mg/m^2 as IV infusion in 26 pts; CDDP 75 mg/m^2 given IV in 28 pts	26% *vs.* 50% experienced neurotoxicity; 37% *vs.* 78% experienced oliguria	CR + PR rates were 70% *vs.* 59%; CR rates were 22% and 11%; no survival rates reported; no statistical analysis due to small sample size	GSH group had less neurotoxicity and oliguria, and higher tumor response rates than the control group	1
Cascinu *et al.*, 1995[33]	Advanced gastric carcinoma	n = 50, 25 chemo + GSH, 25 chemo + placebo	1,500 mg/m^2, given IV over 15 min, immediately before chemo	CDDP 40 mg/m^2 and 5FU 500 mg/m^2 given IV, 4-epidoxorubicin, IV bolus, 9 weekly treatments	17% *vs.* 89% experienced neurotoxicity (p = .0001); other toxicities were similar between the two groups	CR + PR rates were 76% *vs.* 52%; CR rates were 20% and 12%; survival rates were 14 *vs.* 10 months	GSH group had significantly less neurotoxicity and higher tumor response rates than the control group	5
Colombo *et al.*, 1995[34]	Relapsed, advanced ovarian cancer	n = 33, 16 chemo + GSH, 17 chemo alone	2,500 mg/m^2 given IV over 15 min, immediately before chemo	CDDP 50 mg/m^2, 9 weeks as IV infusion	13% *vs.* 27% experienced neuropathy; other toxicities were similar between the two groups	CR + PR rates were 75% *vs.* 60%; CR rates were 44% and 27%; survival rates were 21 *vs.* 15.9 months	GSH group had less neuropathy and higher tumor response rates than the control group	2

TABLE I – RANDOMIZED CLINICAL TRIALS WITH GLUTATHIONE (GSH) AND CHEMOTHERAPY (CONTINUED)

Reference	Tumor type(s)	No. of pts	GSH protocol	Chemotherapy regimen	Toxicity mitigation in GSH group *vs.* Control group	Responses in GSH group *vs.* Control group	Conclusion	Jadad score
Parnis *et al.*, 1995[35]	Advanced ovarian cancer	$n = 24$	1,500 mg/m^2 given IV 15 min prior to chemo	CDDP 40 mg/m^2 over 2-h for either 2,3 or 4 days every 4 weeks	No statistical difference in toxicities between antioxidant and control groups.	n/a	GSH failed to reduce toxicities based on short ½ life.	2
Catalano *et al.*, 2001[36]	Colorectal Cancer	$n = 52$	1,500 mg/m^2 given IV 15 min prior to chemo OR saline placebo	Oxaliplatin 100 mg/m^2 2-h infusion d1, leucovorin 250 mg/m^2 2-h infusion followed by 5-FU 1500 mg/m^2 24-h infusion d1-2, q 2 wks.	No difference after 4 cycles. After 6–8 cycles, 63% exp. Grade 2–4 neurotox in control *vs.* 9.5% exp. Grade 2–4 neurotox in GSH group ($p = 0.001$).	n/a	GSH reduced incidence of moderate to severe neurotoxicity.	2
Fujimoto *et al.*, 1983[37]	Gastric Cancer	$n = 207$	30 mg/kg given IV every day from start of chemo to discharge	5-FU prodrug (FT-207) 16 mg/kg/day IV until discharge, then 12 mg/kg/day orally for 24-36 mos.	No significant difference in GI toxicities, higher serum 5-FU levels in GSH group	Similar survival rates	GSH group had no differences in toxicity, but significantly higher survival rates for stage III patients.	1
Choi *et al.*, 2007[38]	Advanced or metastatic cancers	$n = 51$	30 g/day given orally 3 days prior to chemo and 15 days after	LV 100mg/m^2 IV over 30 min then FU 500 mg/m^2 cont. infusion for 5 days	9% GSH *vs.* 38% control exp. Grade 2-4 mucositis/stomatitis ($p < 0.001$)	n/a	GSH prevented severe mucositis/stomatitis.	2
Wang *et al.*, 2007[39]	Colorectal Cancer	$n = 86$	30 g/day given orally for 7 days every 2 weeks on first day of chemo	Oxaliplatin 85 mg/m^2 IV days 1 and 15 plus folinic acid 20 mg/m^2 over 10-20 min, followed by 500 mg/m^2 bolus 5-FU days 1,8, 15.	After 6 cycles, GSH group had less neuropathy, particularly grade 3–4 11.9% *vs.* 31.8% ($p = 0.04$) and fewer GSH patients (7.1%) needed dose reductions than control (27.3%) ($p = 0.02$)	Similar survival rates, CR rates 52% GSH *vs.* 48% control	GSH significantly reduced incidence and severity of neuropathy as well as the need for dose reduction of oxaliplatin.	1

CR = complete response (or complete remission); SD = stable disease; PR = partial response; NS = non-significant; n/a = not applicable; QoL (quality of life) scores included depression, nausea, vomiting, tingling of hands/feet, shortness of breath, difficulty with concentration, housekeeping and shopping; NSCLC = non-small cell lung cancer; HNC = head and neck cancers; GI = gastrointestinal cancers; CML = chronic myelogenous leukemia; Anticancer drugs and supplements: CDDP = cisplatin; VP-16 = etoposide; GEM = gemcitabine; DOX = doxorubicin; 5FU = fluorouracil; FA = folinic acid (leucovorin); irinotecan = CPT-11; TAM = tamoxifen; NAC = *N*-acetylcysteine; Not all toxicity data is reported, please refer to the text.

TABLE II – RANDOMIZED CLINICAL TRIALS WITH MELATONIN (MLT) AND CHEMOTHERAPY

Reference	Tumor type(s)	No. of pts	MLT protocol	Chemotherapy regimen	Toxicity mitigation in MLT group *vs.* Control group	Responses in MLT group *vs.* Control group	Conclusion	Jadad Score
Lissoni *et al.*, 2003[40]	Advanced NSCLC	$n = 100$, 50 chemo + MLT, 50 chemo alone	20 mg orally in evening	CDDP 20 mg/m^2 as IV infusion for 3 days; etoposide 100 mg/m^2/day IV for 3 days	18% *vs.* 41% experienced neurotoxicity ($p < 0.01$); 14% *vs.* 20% experienced thrombocytopenia ($p < 0.01$); 6% *vs.* 41% experienced weight loss > 10% ($p < 0.001$); 8% *vs.* 35% experienced asthenia ($p < 0.005$)	CR + PR rates were 35% *vs.* 18% ($p < 0.05$); CR rates were 4% *vs.* 0%); no control pts alive after 2 yrs, while 6% in the MLT group were alive after 5 years ($p < 0.001$)	MLT group had significantly reduced toxicities and improved tumor response and survival rates and *vs.* control group	1
Cerea *et al.*, 2003[41]	Met. colorectal cancer	$n = 30$, 14 chemo + MLT, 16 chemo alone	20 mg orally in evening	CPT-11 given IV at 125 mg/m^2 per wk for 9 consecutive wks	29% *vs.* 38% experienced diarrhea grade 3–4 (associated with 50% dose reduction) (NS)	CR + PR rates were 36% *vs.* 13% (NS); neither group reported a CR; survival rates not reported	Toxicities were reduced in MLT group, but not statistically significant; significant disease control in MLT *vs.* control group (86% *vs.* 44%, $p < 0.05$	2
Lissoni *et al.*, 1999[42]	Advanced NSCLC, Breast cancer, GI tumors, HNC	$n = 250$, 104 NSCLC; 77 breast ca; 42 GI tract cancer; 27 HNC	20 mg orally in evening	NSCLC: CDDP + VP-16 or GEM alone, Breast cancer: DOX or mitoxantrone or paclitaxel alone, GI tumors: 5FU, FA, HNC: 5FU + CDDP. No doses given.	20% *vs.* 43% experienced myelosupression ($p < 0.001$); 2% *vs.* 13% experienced neurotoxicity ($p < 0.05$); 2% *vs.* 10% experienced cardiotoxicity ($p < 0.02$); 10% *vs.* 30% experienced stomatitis ($p < 0.02$); 27% *vs.* 63% experienced asthenia ($p < 0.001$)	CR + PR rates were 34% *vs.* 15% ($p < 0.001$); CR rates were 5% and 0% ($p < 0.02$); 1-yr survival rates were 51% *vs.* 23% ($p < 0.001$)	MLT group had significantly reduced toxicities *vs.* control group and significantly improved tumor response and survival rates *vs.* control group.	3
Lissoni *et al.*, 1997[43]	Advanced NSCLC	$n = 70$, 34 chemo + MLT, 36 chemo alone	20 mg orally in evening	CDDP 20 mg/m^2 as IV infusion for 3 days; VP-16 100 mg/m^2/day IV for 3 days	12% *vs.* 36% experienced myelosuppression ($p < 0.05$); 0% *vs.* 14% experienced neuropathy ($p < 0.05$); 9% *vs.* 33% experienced asthenia ($p < 0.01$); and 0% *vs.* 44% experienced weight loss > 10% ($p < 0.001$)	CR + PR rates were 32% *vs.* 17% (NS); CR rates were 3% *vs.* 0%); 1-yr survival rates were 44% *vs.* 19% ($p < 0.05$)	MLT group had significantly reduced toxicities *vs.* control group and significantly higher 1-yr survival rates *vs.* control group;	1

TABLE II – RANDOMIZED CLINICAL TRIALS WITH MELATONIN (MLT) AND CHEMOTHERAPY (CONTINUED)

Reference	Tumor type(s)	No. of pts	MLT protocol	Chemotherapy regimen	Toxicity mitigation in MLT group *vs.* Control group	Responses in MLT group *vs.* Control group	Conclusion	Jadad Score
Lissoni *et al.*, 1997[44]	Met. solid tumors	$n = 80$, lung = 35; BC = 31; GI = 14	20 mg/day orally in evening	Lung (CDDP/VP-16); BC (mitoxantrone); GI (5-FU plus folates). No doses given.	MLT group sign less malaise, asthenia and thrombocytopenia. Stomatitis/neuropathy less (ns). Alopecia/ vomiting not influenced by MLT.	n/a	MLT may prevent myelosuppresion and neuropathy.	1
Ghielmini *et al.*, 1999[45]	Prev. untreated, inoperable Lung cancer pts	$n = 20$	40 mg orally in evening for 21 days, starting 2 days b/f chemo	Carboplatin (5 areas under the curve) for two cycles on day 1, VP-16 (150 mg/m^2 IV) days 1–3 every 4 weeks.	No significant difference in hematological parameters of toxicity.	n/a	MLT not protective against myelotoxic effects of carboplatin and etoposide.	4
Lissoni 2007[46]	Met. NSCLC or GI cancer	$n = 370$	20 mg/day orally in evening	NSCLC: (CDDP/ VP-16 or CDDP/ GEM); CRC: (OXA/5FU and folates); GI: PELF regimen or 5-FU and FA. No doses given	MLT group had less thrombocytopenia 4% *vs.* 22% ($p < 0.01$), neurotoxicity 5% *vs.* 12% ($p < 0.05$), asthenia 27% *vs.* 52% ($p < 0.01$), cachexia 5% *vs.* 20% ($p < 0.005$)	CR + PR rates were 36% *vs.* 20% ($p < 0.001$); 2-yr survival rates 25% *vs.* 13% ($p < 0.05$)	MLT group experienced significantly lower levels of toxicity *vs.* control.	1

CR = complete response (or complete remission); SD = stable disease; PR = partial response; NS = non-significant; n/a = not applicable; QoL (quality of life) scores included depression, nausea, vomiting, tingling of hands/feet, shortness of breath, difficulty with concentration, housekeeping and shopping; NSCLC = non-small cell lung cancer; HNC = head and neck cancers; GI = gastrointestinal cancers; CML = chronic myelogenous leukemia; Anticancer drugs and supplements: CDDP = cisplatin; VP-16 = etoposide; GEM = gemcitabine; DOX = doxorubicin; 5-FU = fluorouracil; FA = folinic acid (leucovorin); irinotecan = CPT-11; TAM = tamoxifen; NAC = N-acetylcysteine; PELF = CDDP, epirubicin, 5-FU and FA; b/f = before; Not all toxicity data is reported, please refer to the text.

TABLE III – RANDOMIZED CONTROLLED TRIALS WITH VITAMIN E

Reference	Tumor type(s)	No. of pts	Antioxidant protocol	Chemotherapy regimen	Toxicity mitigation in Antioxidant group *vs.* Control	Responses in Antioxidant *vs.* Control group	Conclusion	Jadad Score
Pace *et al.*, 2003[47]	Various malignant tumors: lung (15), HNC (5), ovarian (3), urethral (2), gastric (1), testicular (1)	$n = 27$, 13 chemo + vitamin E *vs.* 14 chemo alone	300 mg/d, alpha-tocopherol orally before chemo; then cont'd. for 3 months after treatment	CDDP administered in varying doses and schedules based on specific tumor site, e.g., for lung cancer, 75 mg/m^2 IV on day 1 and GEM 1000 mg/m^{2IV} on day 1 and day 8 every 3 weeks	30.7% *vs.* 85.7% experienced neurotoxicity ($p < .01$); other toxicities were similar between the two groups	CR + PR rates were 62% *vs.* 73% (NS); CR rates and survival rates were not reported	Vitamin E group had a significant reduction in severity and incidence of neurotoxicity. Control group had higher tumor response rate than vitamin E group.	2
Wadleigh *et al.*, 1992[48]	17 solid tumors, 1 acute leukemia	$n = 18$	400 mg/ml topical when lesions were observed	Receiving various chemos	6/9 Vit E pts had complete resolution of oral lesions *vs.* 1/9 control ($p = 0.025$)	n/a	Vit E may be effective in treatment of chemo-induced mucositis.	2
Whittaker and Al-Ismail, 1984[49]	Acute myeloid leukemia	$n = 63$	200 mg Vit E (alpha tocopherol) per day, thrice orally, average 25mg/day orally digoxin or nothing.	Doxorubicin 30 mg/m^2 IV over 5 mins on 5th and 6th days, then maintained at 45 mg/m^2 IV monthly for at least one year	Systolic time interval measurements suggested protective role for digoxin over control ($p < 0.05$).	n/a	Alpha-tocopherol showed no cardiac protective effect.	1
Argyriou *et al.*, 2006[50]	Solid or non-myeloid malignancy	$n = 30$ (completed; 40 enrolled)	600 mg/day orally during chemo and for 3 months after.	Cisplatin-based therapy	Neurotoxicity experienced in 3/14 (21.4%) Vit E pts *vs.* 11/16 (68.5%) control. $p = 0.026$.	n/a	Vit E may have important neuroprotective effects.	3
Argyriou *et al.*, 2006[51]	Solid or non-myeloid malignancy	$n = 32$	300 mg/2x per day orally	Either 175 mg/m^2 IV paclitaxel plus carboplatin at an AUC of 6 on day 1, or 175 mg/m^2 IV paclitaxel plus 80 mg/m^2 epirubicin on day 1.	Neurotoxicity exp. In 3/16 (18.7%) vit E pts *vs.* 10/16 (62.5%) in control ($p = 0.03$). PNP score (neurotoxicity measurement) vit E 2.25 *vs.* control 11 ($p = 0.01$).	n/a	Vit E protects from peripheral nerve damage.	2

CR = complete response (or complete remission); SD = stable disease; PR = partial response; NS = non-significant; n/a = not applicable; AUC = area under the curve; QoL (quality of life) scores included depression, nausea, vomiting, tingling of hands/feet, shortness of breath, difficulty with concentration, housekeeping and shopping; NSCLC = non-small cell lung cancer; HNC = head and neck cancers; GI = gastrointestinal cancers; CML = chronic myelogenous leukemia; Anticancer drugs and supplements: CDDP = cisplatin; VP-16 = etoposide; GEM = gemcitabine; DOX = doxorubicin; 5FU = fluorouracil; FA = folinic acid (leucovorin); irinotecan = CPT-11; TAM = tamoxifen; NAC = N-acetylcysteine; Not all toxicity data is reported, please refer to the text.

TABLE IV – RANDOMIZED CLINICAL TRIALS WITH VARIOUS ANTIOXIDANTS AND ANTIOXIDANT COMBINATIONS

Reference	Tumor type(s)	No. of pts	Antioxidant protocol	Chemotherapy regimen	Toxicity mitigation in Antioxidant group *vs.* Control	Responses in Antioxidant *vs.* Control group	Conclusion	Jadad Score
Pathak *et al.*, 2005[52]	Advanced NSCLC (stages IIIb and IV)	n = 136, 64 chemo + mixed antioxidants *vs.* 72 chemo alone	Oral ascorbic acid (6100 mg/day), vitamin E (1050 mg/day) and beta-carotene (60 mg/day)	Paclitaxel (225 mg/m^2 IV as 3-hour infusion on day 1) and carboplatin (dosage based on most recent creatinine clearance value before each chemo cycle)	No statistical difference in toxicities between antioxidant and control groups	CR + PR rates were 37% *vs.* 33% (p = .28); CR rates were 3% *vs.* 0%; 1 yr survival rates were 39% *vs.* 33%; 2 yr survival rates were 16% *vs.* 11% (p = .20)	Antioxidants did not reduce toxicities. No statistically significant difference in response or survival rates between groups, however, antioxidant group had non-significant advantage in both.	2
Falsaperla *et al.*, 2005[53]	Hormone-refractory prostate cancer (chemo naïve)	n = 48 consecutive pts, 24 chemo + Ellagic acid *vs.* 24 chemo alone	Ellagic acid, 180 mg (60 mg every 8 h) taken orally before meals during & between chemo cycles	Vinorelbine (25 mg/mq IV, weekly for 6 wks) and estramustine (280 mg, 3x/day, for 42 days)	33% *vs.* 75% experienced neutropenia ($p < .05$). Data also showed non-statistically significant decrease in anemia, nausea, anorexia, diarrhea, and neuropathy in antioxidant group	CR + PR rates were 58% *vs.* 25%; CR rates were 25% *vs.* 0% (NS); 2-year survival rates were 75% *vs.* 58% (NS)	Ellagic acid group had significantly decreased neutropenia as well as non-statistically significant reductions in other toxicities; also had higher tumor response and 2-yr survival rates.	2
Weijl *et al.*, 2004[54]	Various malignant tumors: testicular (16), osteo-sarcoma (13), GI (6), urogenital (5), H&N (5), melanoma (3)	n = 48 pts, 25 chemo + antioxidants *vs.* 23 chemo + placebo	Oral vitamin C (1 g, L-ascorbic acid), vitamin E (400 mg, as dl-alpha-tocopherol-acetate) and selenium (100 μg), all dissolved in milky white beverage	CDDP by IV in varying dose intensities (highest planned dose: 100 mg/m^2) Each cycle 1-5 days of cytostatic drug infusions repeated every 21 days.	No significant reduction in nephrotoxicity and ototoxicity, except in correlation analysis with respect to plasma antioxidant levels; also, more pts in antioxidant group received highest planned CDDP dosages.	CR + PR rates were 44% *vs.* 48%; CR rates were 36% *vs.* 26%; survival rates were not reported	More pts in antioxidant arm were able to receive optimal doses of CDDP. Response rates were similar between the two groups, however, CR rates were higher in antioxidant group than control group; Authors report poor pt adherence (46% of all pts did not drink the antioxidant beverage during the whole study period).	4
Meyskens *et al.*, 1995[55]	CML in chronic phase (persistent leukocytosis of at least 30,000 mm^3 found on at least 2 occasions)	n = 124, 57 chemo + vitamin A *vs.* 67 chemo alone	Oral vitamin A (50,000 IU/day, as retinol)	Intermittent oral pulse busulfan: 8 mg/m^2 for 4 days every 4 weeks until chronic stable phase was reached in terms of leukocyte counts (<50,000 mm^3 and >6000 mm^3; chemo restarted when counts reached 50,000 mm^3)	23% *vs.* 4% experienced more grade 2+ toxicities (p = .002)	No tumor response rates were reported; 5-yr survival: 48% *vs.* 30%; after adjustment for survival-related factors	Only study where antioxidant group experienced significantly more toxicities than control group. Significantly greater risk of disease progression (53%; p = .022) and death (60%; P = .014) in chemo alone group *vs.* vitamin A supplemented patients; Vitamin A had higher 5-yr survival rates *vs.* control group.	2

TABLE IV – RANDOMIZED CLINICAL TRIALS WITH VARIOUS ANTIOXIDANTS AND ANTIOXIDANT COMBINATIONS (CONTINUED)

Reference	Tumor type(s)	No. of pts	Antioxidant protocol	Chemotherapy regimen	Toxicity mitigation in Antioxidant group *vs.* Control	Responses in Antioxidant *vs.* Control group	Conclusion	Jadad Score
Myers *et al.*, 1983[56]	Various malignant tumors: breast, lymphoma, soft-tissue sarcoma	$n = 24$, 12 chemo + NAC *vs.* 12 chemo alone	NAC, oral, 5.5 gm/m^2 prior to each chemo treatment	Doxorubicin, 75 mg/m^2 IV every 4 wks	NAC group experienced slightly more toxicities (nausea, alopecia, diarrhea, leucopenia) *vs.* control group	CR + PR rates were 17% *vs.* 7%; CR rates were 4% *vs.* 0%; no survival rates were reported; no statistical analysis was conducted due to diversity of tumor types	NAC group experienced slightly more toxicities *vs.* control group and had higher tumor response rates *vs.* control group	2
Lin *et al.*, 2006[57]	Stage III Colon Cancer	$n = 14$, NAC group = 5, placebo = 9	NAC, oral, 1200 mg	85 mg/m^2 IV oxaliplatin biweekly, and weekly IV bolus of 425 mg/m^2 IV 5-FU and 20 mg/m^2 LV	After 12 cycles, NAC pts 1/5 grade 2-4 neuropathy *vs.* control pts 8/9 grade 2–4 neuropathy ($p < 0.05$)	n/a	NAC reduces incidence of neuropathy.	1
Waldner *et al.*, 2006[58]	Non-Hodgkins Lymphoma	$n = 40$	L-carnitine, 3g/day IV prior to chemo, then 1g/day oral for 21 days after.	CHOP (day 1: 750 mg/m^2 IV cyclophosphamide, 1.4 mg/m^2 IV vincristine and 50 mg/m^2 IV doxorubicin, days 2–5: 100 mg oral prednisolone)	No cardiotoxicity detected in carnitine or placebo group.	n/a	Carnitine improved oxidative metabolism however, not a clinically relevant outcome.	1
Iarussi *et al.*, 1994[59]	Children with leukemia or non-Hodgkins lymphoma	$n = 20$	Co-Q10, 100 mg orally twice daily.	Anthracyclines (cumulative dose fixed at 240 mg/m^2=120 mg/m^2 IV daunorubicin and 120 mg/m^2 IV doxorubicin)	Co-Q10 group had left ventricular fraction shorter than control.	n/a	Protective effect of Co-Q10 on cardiac function with anthracyclines.	2
Sieja and Talerczyk, 2004[60]	Ovarian Cancer	$n = 62$	Se for study group in addition to orally taken mix of β-carotene, vit c, vit E, vit B2, vit B3, for both.	100 mg/m^2 IV CDDP and 600 mg/m^2 IV cyclophosphamide	Significant increase in WBC in Se group ($p < 0.001$); Sig. decrease in all side effects, except diarrhea.	n/a	Beneficial effects of Se found when taken w/chemo.	2
Federico *et al.*, 2001[61]	Cancer of digestive tract	$n = 60$	Oral Se (200 *u*g/day) plus Zinc (21 mg/day) for 50 days	500 mg/m^2 IV MTX day 1, 250 mg/m^2 IV 5-FU day 2, and 600 mg/m^2 IV L-folinic acid day 2.	All pts malnourished at baseline. 21/30 (70%) Sel. Group did not exp. Further decline, but had increase in appetite. 24/30 (80%) control had sig decline of all parameters (body wt, etc.) ($p > 0.01$)	n/a	Se plus Zinc may improve general clinical course.	1

CR = complete response (or complete remission); SD = stable disease; PR = partial response; NS = non-significant; n/a = not applicable; QoL (quality of life) scores included depression, nausea, vomiting, tingling of hands/feet, shortness of breath, difficulty with concentration, housekeeping and shopping; NSCLC = non-small cell lung cancer; HNC = head and neck cancers; GI = gastrointestinal cancers; CML = chronic myelogenous leukemia; Anticancer drugs and supplements: CDDP = cisplatin; VP-16 = etoposide; GEM = gemcitabine; DOX = doxorubicin; 5FU = fluorouracil; FA = folinic acid (leucovorin); irinotecan = CPT-11; TAM = tamoxifen; NAC = N-acetylcysteine; MTX = methotrexate; Not all toxicity data is reported, please refer to the text.

2+ than the control, although these results were not surprising due to the well documented toxicities of high-dose vitamin A.[55] In addition, the general toxicities named in this study were not reported by any other studies reviewed. In another study (NAC) that reported higher toxicities in the antioxidant group than the control group, 2 of 8 side effects measured were nonsignificantly higher in the antioxidant group. One of the 2 reported increased toxicities was diarrhea, a known side effect of oral NAC supplementation.[56] In the cases of myelosuppression,[30,40,42–44,46,53,60] asthenia,[40,42–44,46,60,61] weight loss,[31,40,43,46] cardiotoxicity[42,59] and nephrotoxicity,[42] decreased toxicities were statistically significant in every report.

The most frequently investigated toxicity was neurotoxicity in (19), a major side effect of platinum-based chemotherapies. Of 19 total assessments of neuropathy, 15 reported decreased neurotoxicity in the antioxidant group.[29,32–34,36,39,40,42–44,46,47,50,51,57] Of these 15 reports of decreased neurotoxicity, 12 were statistically significant.[29,33,36,39,40,42,43,46,47,50,51,57] No studies reported increased neurotoxicities from antioxidant supplementation.

Myelosuppression was the second most frequently investigated toxicity with 17 assessments, 8 of which reported significantly decreased toxicities in the antioxidant group.[30,40,42–44,46,53,60] However, 9 studies reported no difference between the incidence of myelosuppression in the antioxidant group and the control group.[31,33,34,37,45,48,52,55,56] Other toxicities reported to be the same between the 2 groups were alopecia,[33,40,43,44,50–52] diarrhea,[43,52,53] nausea/vomiting,[44,50,51,56] nephrotoxicity[43,54] and ototoxicity.[34,35,54]

Given these findings, it appears that some antioxidant nutrients may be more effective than others at preventing or alleviating treatment-related toxicities. Vitamin A and L-carnitine, for example, are considered weak antioxidants, perhaps accounting for their lack of toxicity-mitigating effects. Additionally, the potentially cytoprotective effects of antioxidants may be dose-dependent or possibly require appropriate synergists to amplify cytoprotective effects. The positive findings of the glutathione studies may result in part from intravenous administration of the antioxidant, allowing for high doses of the antioxidant. As a result of some investigators' concerns that antioxidants may interfere with the efficacy of chemotherapy, doses of antioxidants may have been administered at suboptimal levels. Future studies should consider a range of doses for antioxidant supplements given concurrently with chemotherapy.

While this review only included studies with chemotherapy regimens of at least one drug thought to produce higher levels of oxidative stress (*e.g.*, anthracyclines, platinum coordination complexes), there is some indication that these free-radical producing drugs may have additional mechanisms of action.[62] Thus, while antioxidants may have reduced free-radical damage to normal tissues and potentially diminished side effects, other non-oxidative mechanisms of action of the chemotherapy may still produce toxicities unaffected by antioxidant supplementation.

Tumor response rates were not the focus of this review, however it is noteworthy that all but one[47] of the antioxidant supplemented groups in studies reporting tumor response experienced the same or better response than the control group. No studies reported significantly worse survival or response in the antioxidant supplement group, as reported in our previous publication, which reviewed studies that reported tumor response or survival.[14] Overall, MLT, vitamin E and GSH showed consistent and promising reductions in toxicities, in particular, neurotoxicity. Of the MLT and vitamin E studies that reported neurotoxicity data, all but one[44] reported a statistically significant reduction in neurotoxicities in the antioxidant supplemented group over the control group. Additionally, the MLT studies, while of different tumor types and a range of sample sizes (20–370), showed a consistent reduction in myelosuppression. Every MLT study was conducted with 20 mg of MLT taken orally in the evening, beginning 7 days prior to chemotherapy,[40–44,46] except the Ghielmini study[45] which gave 40 mg orally in the evening, beginning 2 days prior to chemotherapy. The Ghielmini study was the smallest MLT study with only 20 patients and was the only MLT study that did not show a reduction of myelosuppression. All but one of the other studies showed a statistically significant reduction in myelosuppression. While the studies that reported a reduction in myelosuppression did not receive high Jadad scores, the sample sizes were some of the largest of all the studies included in this review. Two important factors to be determined by future studies are the optimal dose of MLT as well as the optimal start date of initial MLT treatment from the outset of chemotherapy. Furthermore, while these MLT studies are consistent in their larger sample sizes, dosing and results, all but one were conducted by a single research group. Replication of the findings by other investigators is urgently needed.

Four of the 5 vitamin E studies showed statistically significant reductions in toxicities, primarily neurotoxicities. Doses ranged from 300–600 mg of vitamin E across various cancer types. The quality of the studies spanned from Jadad scores of 3 to one study which scored a one. Of note, the study of the lowest quality was the only study to not report a statistically significant decrease in toxicity. This study by Whittaker recruited 63 patients, but only 25 (7 on vitamin E) survived to be included in statistical analysis for "cardiac damage."[49] Because none of the vitamin E studies had high Jadad scores or large sample sizes, statistically significant reductions in toxicities reported by the other 4 studies cannot be generalized for clinical use. Future studies should employ larger samples and better methodology.

Finally, while the GSH studies spanned from some of the highest quality studies within the review to some of the lowest, GSH appears to be one of the most promising antioxidants for the reduction of neurotoxicity from platinum-based chemotherapy. Unfortunately, there was little consistency among the studies with various tumor types, sample sizes, doses and routes of administration (IV and oral, 1,500 mg/m^2 to 30 g/day p.o.). However, those studies of the highest quality reported a reduction in neurotoxicity, 2 of which were statistically significant.[29,33] GSH should be further studied for its potential to reduce neurotoxicities for patients on platinum-based chemotherapy, in particular, for colorectal and gastric cancers. However, future research on concurrent use of antioxidants and chemotherapy should employ larger sample sizes, single cancer types and better research designs.

Study limitations

This summary of 33 RCTs encompassed cancer patients of diverse tumor and treatment type. All but one of the studies included less than 300 patients and therefore should generally be regarded as Phase II studies. Larger sample sizes are necessary in order to reliably assess modest yet clinically important treatment effects. Some studies identified in this review may have been designed and powered to detect differences in treatment response or survival rather than toxicity. Lack of adequate statistical power to detect differences in toxicities would render those studies showing similar or non-significantly better results in the antioxidant arms difficult to interpret. In the absence of statistical power calculations (either a priori or post hoc), a common problem in older randomized trials, other clinically important effects may have been missed in the smaller trials.[63] The limited number and power of the studies included make it impractical to conclusively rule out the possibility that antioxidants have no effect or even a negative effect on chemotherapy toxicities. To exclude this possibility, very large and well-designed trials would have to be carried out.

Other limitations include the predominately advanced stage of the patients participating in these studies and compliance issues. Because the majority of the subjects in the included studies had advanced or relapsed disease; the applicability of these results in patients with earlier, more chemosensitive disease is not addressed by these studies. Noncompliance was an issue in only 1 study, resulting in a 46% noncompliance rate among the antioxidant group.[54]

While quality of the studies was assessed using the Jadad method, this method is not without limitations. It is useful in its assessment of a randomized trial's methodological quality, yet, it

fails to take into account limitations of studies such as sample size and statistical power. In this review, the Jadad method was particularly pertinent due to the lack of blinding or placebo controls in many of the studies; less than one-third of the studies (10) included double-blinded, placebo-controlled methods.[29,31,33,35,36,45,48,50,54,60] Of the studies that did use double-blinding, 6 evaluated neurotoxicity, 4 of which reported a statistically significant reduction of neurotoxicity in the antioxidant supplemented groups.[29,33,36,50] In addition, the response rates were similar to or non-significantly greater in antioxidant groups than those of control groups in all 4 studies.

Lastly, while extensive efforts were made to comprehensively review the literature through searching multiple databases, hand searching reference lists, personal communications, etc., extending the search to include hand searching of conference proceedings, dissertations and theses and additional clinical trial registries may have further reduced bias and possibly produced more negative studies.

Implications for clinical practice

This systematic review provides preliminary evidence, limited by quality and sample size of the reviewed studies, suggesting that certain antioxidant supplements may reduce adverse reactions including neurotoxicity, asthenia, stomatitis/mucositis, and weight loss. Significant reductions in toxicity may alleviate dose-limiting toxicities so that more patients are able to successfully complete prescribed chemotherapy regimens, suggesting an improved therapeutic index. The aforementioned study by Neugut *et al*.[25] demonstrated the relationship between more doses of chemotherapy and higher survival rate. In this systematic review, 5 included studies reported the antioxidant group (3 GSH, MLT and a mixture) experienced better treatment tolerance in terms of either less dose-reduction[34,39,41,54] or higher rates of completing full chemotherapy regimens than control groups (GSH).[31] None of the included studies reported that the control group had higher doses or more full cycles of chemotherapy than the antioxidant group. Because of the potential for the relationship between the reduction of dose-limiting toxicities allowing for full chemotherapy cycles and the subsequent potential for increased tumor response and/or survival, it is critical that future antioxidant/chemotherapy studies employ proper sample sizes and methodologies so that the results are of clear clinical relevance.

Our previous review found no evidence of antioxidant interference with chemotherapy mechanisms, with a possibility that antioxidants may even improve tumor response or patient survival.[14] Combining this result with the potential for improvement of toxic side effects by antioxidants reported in the present review, additional strategies for further research on antioxidants and chemotherapy are now warranted. First, toxicities should be chosen that occur regularly in high percentages of patients, are clinically significant in terms of requiring dose reductions or impairing quality of life, and are poorly controlled by currently available means. Accurate means for measuring the toxicities of interest should be available. Neurotoxicity from platinum-based drugs (which have strong ROS mechanisms of action) may be one appropriate model to research. Animal studies might be employed to select antioxidants and modes of administration that have the highest probabilities of clinical success. Subsequently, clinical trials progressing through Phase I, II and III models could be undertaken. This would advance the present state of knowledge regarding antioxidants and chemotherapy from the existing series of Phase II-type studies towards a more thorough assessment. Finally, most studies to date have been performed in patients with advanced or relapsed disease. For these patients, an improved therapeutic index is of special relevance to allow continuation of chemotherapy, since lengthy chemotherapy regimens may be applied to retard disease progression even in the absence of complete remission. Thus, regimens for advanced disease, or second-line and later regimens may be of particular interest to evaluate in future research.

References

1. Boon H, Stewart M, Kennard MA, Gray R, Sawka C, Brown JB, McWilliam C, Gavin A, Baron RA, Aaron D, Haines-Kamka T. Use of complementary/alternative medicine by breast cancer survivors in Ontario: prevalence and perceptions. J Clin Oncol 2000;18:2515–21.
2. Burstein HJ, Gelber S, Guadagnoli E, Weeks JC. Use of alternative medicine by women with early-stage breast cancer. N Engl J Med 1999;340:1733–9.
3. Gupta D, Lis CG, Birdsall TC, Grutsch JF. The use of dietary supplements in a community hospital comprehensive cancer center: implications for conventional cancer care. Support Care Cancer 2005;13: 912–9.
4. Kumar NB, Hopkins K, Allen K, Riccardi D, Besterman-Dahan K, Moyers S. Use of complementary/integrative nutritional therapies during cancer treatment: implications in clinical practice. Cancer Control 2002;9:236–43.
5. Lee MM, Lin SS, Wrensch MR, Adler SR, Eisenberg D. Alternative therapies used by women with breast cancer in four ethnic populations. J Natl Cancer Inst 2000;92:42–7.
6. Molassiotis A, Fernandez-Ortega P, Pud D, Ozden G, Platin N, Hummerston S, Scott JA, Panteli V, Gudmundsdottir G, Selvekerova S, Patiraki E, Kearney N. Complementary and alternative medicine use in colorectal cancer patients in seven European countries. Complement Ther Med 2005;13:251–7.
7. Molassiotis A, Ozden G, Platin N, Scott JA, Pud D, Fernandez-Ortega P, Milovics L, Panteli V, Gudmundsdottir G, Browall M, Madsen E, Patiraki E, et al. Complementary and alternative medicine use in patients with head and neck cancers in Europe. Eur J Cancer Care (Engl) 2006;15:19–24.
8. Molassiotis A, Scott JA, Kearney N, Pud D, Magri M, Selvekerova S, Bruyns I, Fernadez-Ortega P, Panteli V, Margulies A, Gudmundsdottir G, Milovics L, et al. Complementary and alternative medicine use in breast cancer patients in Europe. Support Care Cancer 2006;14:260–7.
9. Richardson MA, Sanders T, Palmer JL, Greisinger A, Singletary SE. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. J Clin Oncol 2000;18:2505–14.
10. VandeCreek L, Rogers E, Lester J. Use of alternative therapies among breast cancer outpatients compared with the general population. Altern Ther Health Med 1999;5:71–6.
11. Verhoef M, Balneaves L, Boon H, Vroejindewey A. Reasons for and characteristics associated with complementary and alternative medicine use among adult cancer patients: a systematic review. Integr Cancer Ther 2004;3:1–12.
12. D'Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. CA Cancer J Clin 2005;55:319–21.
13. Conklin KA. Chemotherapy-associated oxidative stress: impact on chemotherapeutic effectiveness. Integr Cancer Ther 2004;3:294–300.
14. Block KI, Koch AC, Mead MN, Tothy PK, Newman RA, Gyllenhaal C. Impact of antioxidant supplementation on chemotherapeutic efficacy: a systematic review of the evidence from randomized controlled trials. Cancer Treat Rev 2007;33:407–18.
15. Alberts DS, Noel JK. Cisplatin-associated neurotoxicity: can it be prevented? Anticancer Drug 1995;6:369–83.
16. Taguchi T, Nazneen A, Abid MR, Razzaque MS. Cisplatin-associated nephrotoxicity and pathological events. Contrib Nephrol 2005;148:107–21.
17. Hrelia S, Bordoni A, Angeloni C, Leoncini E, Biagi P. Nutritional interventions to counteract oxidative stress in cardiac cells. Ital J Biochem 2004;53:157–63.
18. Hardman J, Limbird L, Molinoff P, Ruddon R, Gilman A. Goodman and Gilman's "the pharmacological basis of therapeutics," 9th edn. New York: McGraw Hill, 1996.
19. Ladas EJ, Jacobson JS, Kennedy DD, Teel K, Fleischauer A, Kelly KM. Antioxidants and cancer therapy: a systematic review. J Clin Oncol 2004;22:517–28.
20. Almushatat AS, Talwar D, McArdle PA, Williamson C, Sattar N, O'Reilly DS, Underwood MA, McMillan DC. Vitamin antioxidants, lipid peroxidation and the systemic inflammatory response in patients with prostate cancer. Int J Cancer 2006;118:1051–3.
21. Diakowska D, Lewandowski A, Kopec W, Diakowski W, Chrzanowska T. Oxidative DNA damage and total antioxidant status in serum of patients with esophageal squamous cell carcinoma. Hepatogastroenterology 2007;54:1701–4.
22. Tesarova P, Kalousova M, Trnkova B, Soukupova J, Argalasova S, Mestek O, Petruzelka L, Zima T. Carbonyl and oxidative stress in patients with breast cancer—is there a relation to the stage of the disease? Neoplasma 2007;54:219–24.
23. Erhola M, Toyokuni S, Okada K, Tanaka T, Hiai H, Ochi H, Uchida K, Osawa T, Nieminen MM, Alho H, Kellokumpu-Lehtinen P. Bio-

marker evidence of DNA oxidation in lung cancer patients: association of urinary 8-hydroxy-2′-deoxyguanosine excretion with radiotherapy, chemotherapy, and response to treatment. FEBS Lett 1997; 409:287–91.
24. Sangeetha P, Das UN, Koratkar R, Suryaprabha P. Increase in free radical generation and lipid peroxidation following chemotherapy in patients with cancer. Free Radic Biol Med 1990;8:15–9.
25. Neugut AI, Matasar M, Wang X, McBride R, Jacobson JS, Tsai WY, Grann VR, Hershman DL. Duration of adjuvant chemotherapy for colon cancer and survival among the elderly. J Clin Oncol 2006;24:2368–75.
26. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
27. Gopal R. Non-small cell lung cancer: the role of cytoprotection in treating therapy-related toxicity. J Support Oncol 2004;2:13–7.
28. McCumber LM. The potential influence of cell protectors for dose escalation in cancer therapy: an analysis of amifostine. Med Dosim 2004;29:139–43.
29. Cascinu S, Catalano V, Cordella L, Labianca R, Giordani P, Baldelli AM, Beretta GD, Ubiali E, Catalano G. Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2002;20:3478–83.
30. Schmidinger M, Budinsky AC, Wenzel C, Piribauer M, Brix R, Kautzky M, Oder W, Locker GJ, Zielinski CC, Steger GG. Glutathione in the prevention of cisplatin induced toxicities. A prospectively randomized pilot trial in patients with head and neck cancer and non small cell lung cancer. Wien Klin Wochenschr 2000;112:617–23.
31. Smyth JF, Bowman A, Perren T, Wilkinson P, Prescott RJ, Quinn KJ, Tedeschi M. Glutathione reduces the toxicity and improves quality of life of women diagnosed with ovarian cancer treated with cisplatin: results of a double-blind, randomised trial. Ann Oncol 1997;8:569–73.
32. Bogliun G, Marzorati L, Marzola M, Miceli MD, Cantu MG, Cavaletti G. Neurotoxicity of cisplatin +/− reduced glutathione in first-line treatment of advanced ovarian cancer. Int J Gynecol Cancer 1996;6:415–9.
33. Cascinu S, Cordella L, Del Ferro E, Fronzoni M, Catalano G. Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomized double-blind placebo-controlled trial. J Clin Oncol 1995;13:26–32.
34. Colombo N, Bini S, Miceli D, Bogliun G, Marzorati L, Cavaletti G, Parmigiani F, Venturino P, Tedeschi M, Frattola L, Buratti C, Mangioni C. Weekly cisplatin +/− glutathione in relapsed ovarian carcinoma. Int J Gynecol Cancer 1995;5:81–6.
35. Parnis F, Coleman R, Harper P, Pickering D, Topham C, Whittington J, Tedeschi M. A randomized double-blind placebo controlled clinical trial assessing the tolerability and efficacy of glutathione as an adjuvant to escalating doses of cisplatin in the treatment of advanced ovarian cancer. Eur J Cancer 1995;31A:1721.
36. Catalano V, Cascinu S, Labianca R, Giordani P, Mosconi S, Cordella L, Ubiali E, Baldelli AM, Pessi MA, Catalano G. Neuroprotective effect of glutathione (GSH) on oxaliplatin (L-OHP) based chemotherapy in advanced colorectal cancer patients (pts): a randomized double-blind placebo-controlled trial. Eur J Cancer 2001;37:S280–S281.
37. Fujimoto S, Miyazaki M, Kitsukawa Y, Okui K, Hosaka T, Karaki S, Kawanomoto S. Clinical evaluation of prolonged chemotherapy combined with induction of hepatic drug-metabolizing enzymes as an adjuvant for treating patients with gastric cancer. Jpn J Surg 1983;13:486–92.
38. Choi K, Lee SS, Oh SJ, Lim SY, Lim SY, Jeon WK, Oh TY, Kim JW. The effect of oral glutamine on 5-fluorouracil/leucovorin-induced mucositis/stomatitis assessed by intestinal permeability test. Clin Nutr 2007; 26:57–62.
39. Wang WS, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Chiou TJ, Liu JH, Yen CC, Chen PM. Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients. Oncologist 2007;12:312–9.
40. Lissoni P, Chilelli M, Villa S, Cerizza L, Tancini G. Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial. J Pineal Res 2003;35:12–5.
41. Cerea G, Vaghi M, Ardizzoia A, Villa S, Bucovec R, Mengo S, Gardani G, Tancini G, Lissoni P. Biomodulation of cancer chemotherapy for metastatic colorectal cancer: a randomized study of weekly low-dose irinotecan alone versus irinotecan plus the oncostatic pineal hormone melatonin in metastatic colorectal cancer patients progressing on 5-fluorouracil-containing combinations. Anticancer Res 2003;23:1951–4.
42. Lissoni P, Barni S, Mandala M, Ardizzoia A, Paolorossi F, Vaghi M, Longarini R, Malugani F, Tancini G. Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. Eur J Cancer 1999;35:1688–92.
43. Lissoni P, Paolorossi F, Ardizzoia A, Barni S, Chilelli M, Mancuso M, Tancini G, Conti A, Maestroni GJ. A randomized study of chemotherapy with cisplatin plus etoposide versus chemoendocrine therapy with cisplatin, etoposide and the pineal hormone melatonin as a first-line treatment of advanced non-small cell lung cancer patients in a poor clinical state. J Pineal Res 1997;23:15–9.
44. Lissoni P, Tancini G, Barni S, Paolorossi F, Ardizzoia A, Conti A, Maestroni G. Treatment of cancer chemotherapy-induced toxicity with the pineal hormone melatonin. Support Care Cancer 1997;5:126–9.
45. Ghielmini M, Pagani O, de Jong J, Pampallona S, Conti A, Maestroni G, Sessa C, Cavalli F. Double-blind randomized study on the myeloprotective effect of melatonin in combination with carboplatin and etoposide in advanced lung cancer. Br J Cancer 1999;80:1058–61.
46. Lissoni P. Biochemotherapy with standard chemotherapies plus the pineal hormone melatonin in the treatment of advanced solid neoplasms. Pathol Biol (Paris) 2007;55:201–4.
47. Pace A, Savarese A, Picardo M, Maresca V, Pacetti U, Del Monte G, Biroccio A, Leonetti C, Jandolo B, Cognetti F, Bove L. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. J Clin Oncol 2003;21:927–31.
48. Wadleigh R, Redman R, Graham M, Krasnow S, Anderson A, Cohen M. Vitamin E in the treatment of chemotherapy-induced mucositis. Am J Med 1992;92:481–4.
49. Whittaker JA, Al-Ismail SA. Effect of digoxin and vitamin E in preventing cardiac damage caused by doxorubicin in acute myeloid leukaemia. Br Med J (Clin Res Ed)1984;288:283–4.
50. Argyriou AA, Chroni E, Koutras A, Iconomou G, Papapetropoulos S, Polychronopoulos P, Kalofonos HP A randomized controlled trial evaluating the efficacy and safety of vitamin E supplementation for protection against cisplatin-induced peripheral neuropathy: final results. Support Care Cancer 2006;14:1134–40.
51. Argyriou AA, Chroni E, Koutras A, Iconomou G, Papapetropoulos S, Polychronopoulos P, Kalofonos HP. Preventing paclitaxel-induced peripheral neuropathy: a phase II trial of vitamin E supplementation. J Pain Symptom Manage 2006;32:237–44.
52. Pathak A, Bhutani M, Guleria R, Bal S, Mohan A, Mohanti BK, Sharma A, Pathak R, Bhardwaj NK, Prasad KN, Kochupillai V. Chemotherapy alone *vs*. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. J Am Coll Nutr 2005;24:16–21.
53. Falsaperla M, Morgia G, Tartarone A, Ardito R, Romano G. Support ellagic acid therapy in patients with hormone refractory prostate cancer (HRPC) on standard chemotherapy using vinorelbine and estramustine phosphate. Eur Urol 2005;47:449–54.
54. Weijl NI, Elsendoorn TJ, Lentjes EGWM, Hopman GD, Wipkink-Bakker A, Zwinderman AH, Cleton FJ, Osanto S. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomized, double-blind, placebo-controlled study. Eur J Cancer 2004;40: 1713–23.
55. Meyskens FL, Jr, Kopecky KJ, Appelbaum FR, Balcerzak SP, Samlowski W, Hynes H. Effects of vitamin A on survival in patients with chronic myelogenous leukemia: a SWOG randomized trial. Leuk Res 1995;19:605–12.
56. Myers C, Bonow R, Palmeri S, Jenkins J, Corden B, Locker G, Doroshow J, Epstein S. A randomized controlled trial assessing the prevention of doxorubicin cardiomyopathy by *N*-acetylcysteine. Semin Oncol 1983;10:53–5.
57. Lin PC, Lee MY, Wang WS, Yen CC, Chao TC, Hsiao LT, Yang MH, Chen PM, Lin KP, Chiou TJ. *N*-acetylcysteine has neuroprotective effects against oxaliplatin-based adjuvant chemotherapy in colon cancer patients: preliminary data. Support Care Cancer 2006;14:484–7.
58. Waldner R, Laschan C, Lohninger A, Gessner M, Tuchler H, Huemer M, Spiegel W, Karlic H. Effects of doxorubicin-containing chemotherapy and a combination with L-carnitine on oxidative metabolism in patients with non-Hodgkin lymphoma. J Cancer Res Clin Oncol 2006;132:121–8.
59. Iarussi D, Auricchio U, Agretto A, Murano A, Giuliano M, Casale F, Indolfi P, Iacono A. Protective effect of coenzyme Q10 on anthracyclines cardiotoxicity: control study in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma. Mol Aspects Med 1994; 15S:S207–S12.
60. Sieja K, Talerczyk M. Selenium as an element in the treatment of ovarian cancer in women receiving chemotherapy. Gynecol Oncol 2004;93:320–7.
61. Federico A, Lodice P, Federico P, Del Rio A, Mellone M, Catalano G, Federico P. Effects of selenium and zinc supplementation on nutritional status in patients with cancer of digestive tract. Eur J Clin Nutr 2001;55:293–7.
62. Keizer HG, Pinedo HM, Schuurhuis GJ, Joenje H. Doxorubicin (adriamycin): a critical review of free radical-dependent mechanisms of cytotoxicity. Pharmacol Ther 1990;47:219–31.
63. Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. JAMA 1994;272:122–4.