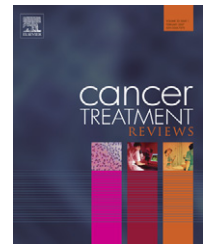




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CONTROVERSY

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

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Summary Purpose: Much debate has arisen about whether antioxidant supplementation alters the efficacy of cancer chemotherapy. Some have argued that antioxidants scavenge the reactive oxygen species integral to the activity of certain chemotherapy drugs, thereby diminishing treatment efficacy. Others suggest antioxidants may mitigate toxicity and thus allow for uninterrupted treatment schedules and a reduced need for lowering chemotherapy doses. The objective of this study is to systematically review the literature in order to compile results from randomized trials that evaluate concurrent use of antioxidants with chemotherapy. **Design:** MEDLINE, Cochrane, CinAhl, AMED, AltHealthWatch and EMBASE databases were searched. Only randomized, controlled clinical trials that reported survival and/or tumor response were included in the final tally. The literature searches were performed in duplicate following a standardized protocol. No meta-analysis was performed due to heterogeneity of tumor types and treatment protocols used in trials that met the inclusion criteria. **Results:** Of 845 articles considered, 19 trials met the inclusion criteria. Antioxidants evaluated were: glutathione (7), melatonin (4), vitamin A (2), an antioxidant mixture (2), vitamin C (1),

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N-acetylcysteine (1), vitamin E (1) and ellagic acid (1). Subjects of most studies had advanced or relapsed disease.

Conclusion: None of the trials reported evidence of significant decreases in efficacy from antioxidant supplementation during chemotherapy. Many of the studies indicated that antioxidant supplementation resulted in either increased survival times, increased tumor responses, or both, as well as fewer toxicities than controls; however, lack of adequate statistical power was a consistent limitation. Large, well-designed studies of antioxidant supplementation concurrent with chemotherapy are warranted.

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Introduction

The use of antioxidant supplements by patients with cancer is estimated between 13% and 87%.^{1–10} This wide range of percentages might be attributed to 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 Patients may take antioxidant supplements while undergoing chemotherapy to help alleviate side effects from toxic chemotherapies and to increase the efficacy of chemotherapy. However, the use of antioxidant supplements by patients undergoing chemotherapy has been criticized due to concerns that the antioxidants may interfere with the mechanism of action of the chemotherapy and subsequently decrease its efficacy.¹² Others argue that antioxidant supplements are useful in conjunction with 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 possibly at higher doses.¹³ As a result, patients may have better tumor response rates and increased chances of survival.

One of the main mechanisms of chemotherapy drugs against cancer cells is the formation of reactive oxygen species (ROS), or free radicals. Drugs with free radical mechanisms 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 ROS often are the source of serious side effects, as well. For example, cisplatin and other platinum-induced toxicities include nephrotoxicity, ototoxicity, and peripheral neuropathy.^{14,15} Doxorubicin and other anthracyclines often cause cardiotoxicity.¹⁶ Other chemotherapy drugs generate lower levels of oxidative stress, and free radical damage is thought to be of less importance in their mechanisms of action. These drugs include the taxanes (e.g. paclitaxel, docetaxel), vinca alkaloids (e.g. vincristine, vinblastine), antimetabolites (e.g. methotrexate, fluorouracil, cytarabine).^{13,17} Examples of chemotherapy drugs that are not believed to depend on oxidative mechanisms for their anticancer effects include asparaginase and dactinomycin. While attempting to char-

acterize chemotherapeutic compounds in this manner facilitates any attempt to understand the complexity of interactions between therapy and antioxidant use, the fact remains that most effective chemotherapeutic agents are multi-mechanistic and their relative ability to generate free radicals is not only dose-dependent but also dependent on the localization and metabolism of the drug within specific tissues. In addition, antioxidants have multiple mechanisms of action, and depending on their use, have been noted to have the potential to serve as oxidant molecules themselves. The supplements included in this review range in their antioxidant mechanisms 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 antioxidants act as metal chelators (Vitamin C, EGCG) or cellular protectors from free radical attack (vitamins A, C, E and melatonin) and some target and repair DNA aberrations (EGCG). Thus, understanding the interactions of selected antioxidants with selected chemotherapeutic agents is difficult enough when using simple *in vitro* cell systems but exceedingly more difficult to interpret in a simple manner when using more complex animal tumor models. Further, aside from their antioxidant activities, these agents may affect the pharmacokinetics or pharmacodynamics of chemotherapy agents. This makes an examination of the role of antioxidants in well-designed randomized clinical trials of clinical importance.

Cancer patients often have low-antioxidant levels before initiating treatment,¹⁸ 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.^{19,20} In theory, antioxidant supplementation during the administration of these chemotherapies would either hinder the cytotoxic mechanism(s) of chemotherapy by quenching reactive oxygen species produced by the drug, or help protect healthy cells from additional oxidative stress and toxicity from treatment. This then represents the heart of the dilemma for patients with cancer in trying to understand whether antioxidant therapy will increase their quality of life through protection of normal tissues or interfere with the eventual clinical outcome of their disease. Alternatively, antioxidants might improve outcomes through increasing

the ability of patients to tolerate full doses of antineoplastics with uninterrupted treatment schedules. This review evaluates randomized, controlled trials in which studies measured survival and/or treatment response levels of patients given antioxidants concurrently with chemotherapy in order to determine if the antioxidants enhanced or interfered with the efficacy of the chemotherapy.

Methods

Electronic databases searched included MEDLINE, CENTRAL (The Cochrane Library), CinAhl, AMED/AltHealthWatch (combined) and EMBASE (all from inception to the last week of December, 2006).²¹ Databases were chosen for their inclusion of alternative and complementary medicine articles. All the databases were searched using the same search string, with the exception of Medline, where the string had to be altered to fit the database's particular terminology. Terms were joined between three categories in attempts to cover as many variations as possible for (1) cancer (5), (2) chemotherapy (24), and (3) antioxidants (32). Authors will provide the detailed search string upon request. Searches were not limited by language. For non-English abstracts, abstracts were translated and if they appeared to meet inclusion criteria, then the entire article was translated into English. Additional references were identified by hand searching the references of key articles and reviews.

Searches were duplicated independently by two researchers (M.M., A.K.) and yielded the following results: MEDLINE (317), AMED/AltHealthWatch (254), CENTRAL (138), CinAhl (90) and EMBASE (46). Initial screening included reading the title and abstract. For articles that passed the initial screening, full-text was obtained. In certain cases, authors were contacted for clarification or additional data. The resulting articles were screened for inclusion according to the following criteria:

Type of study. Only randomized, controlled trials were included in the review. Studies included provided survival data and/or tumor response data.

Study populations. Only cancer patients who were currently undergoing chemotherapy were included. All types of cancer were included, as well as various chemotherapies that utilized the reactive oxygen species mechanism.

Type of therapy. Patients took antioxidants (orally or intravenously) concurrently with chemotherapy. 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. Whole herbs and multicomponent herbal formulas that contained phytochemical antioxidants were not included in the study because of the potential for confounding of results by non-antioxidant activities of complex herbs and mixtures, which is avoided to some extent by the use of antioxidant phytochemical

extracts. For articles that met all inclusion criteria, data were extracted by M.M. and A.K. All data were obtained from published peer-reviewed reports for each trial. The quality of the included articles was assessed in duplicate by A.K. and C.G. according to the Jadad scoring method. This validated scale allows assessment of the methodological quality of each trial by quantifying the study's randomization, blinding methods, and description of patient dropouts/withdrawals, resulting in a score between 0 and 5, with zero indicating a weak study design and five indicating a strong study design.²²

A limitation of the search and subsequent quality assessment of included articles was the dependence on what was available in the written report alone. In certain cases, authors were contacted for verification of randomization. The authors of this paper have attempted to avoid publication bias by performing the searches in duplicate, as well as only including randomized, controlled trials that inherently reduce bias. However, bias in preferential publication of positive trials cannot be excluded.

Results

Of 845 references screened, 19 met the inclusion criteria, with a total of 1554 patients evaluated. A flow chart shows the exclusion factors and numbers of articles for each factor (Fig. 1). Nearly, half of the articles were excluded because they were not randomized, controlled trials (400). In other

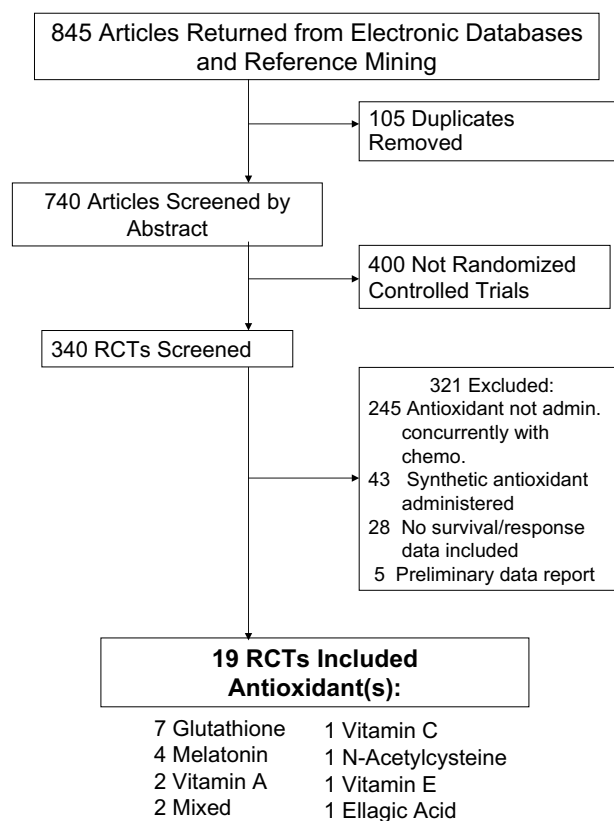


Figure 1 Flow chart of exclusion process for systematic review.

Table 1 Randomized clinical trials with glutathione (GSH) and chemotherapy

Reference	Tumor type(s)	No. of pts	GSH protocol	Chemotherapy regimen	Responses in GSH group versus Control group	Toxicity mitigation in GSH group versus Control group	Conclusion	Jadad Score
Cascinu et al. ²⁶	Advanced colorectal cancer	n = 52 26 chemo + GSH 26 chemo + placebo	1500 mg/m ² , 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	CR + PR rates were 77% versus 23% in GSH versus control groups; neither group reported a CR; Median survival: 16 versus 17 months	30% versus 100% in GSH versus control groups experienced grade 2-4 neurotoxicity (P = .004); were similar between the groups	GSH group experienced significantly reduced neuropathy versus control group	5
Schmidinger et al. ²⁹	Advanced NSCLC and HNC	n = 20 6 with NSCLC 14 HNC; 11 chemo + GSH 9 chemo + placebo	5000 mg/m ² , over 15 min, immediately before chemo	DDP 80 mg/m ² as iv infusion. HNC pts received 450 mg/m ² 5FU by i.v. bolus, NSCLC received 120 mg/m ² i.v. VP-16, with cycles every 4 wks	CR + PR rates were 55% versus 50%; CR rates were 9% and 0%; Median survival: 13.1 months versus 10.5 months	Significant decrease in hemoglobin (P = .04), platelet counts (P = .03), and white blood cell counts (P = .004) in placebo versus GSH groups; neither group experienced neurotoxicity	GSH group had significantly reduced hematological toxicities versus the control group	2
Smyth et al. ³⁰	Ovarian cancer (Stages I-IV)	n = 151 74 chemo + GSH 77 chemo + placebo	3000 mg/m ² , over 15 min, immediately before chemo	DDP 100 mg/m ² as i.v. infusion, every 3 weeks for six courses	CR + PR rates were 73% versus 62% (P = .25); CR rates were 46% versus 9%; survival rates were similar (stated in article)	58% versus 39% were able to receive 6 cycles of CDDP (P = .04); 39% versus 49% experienced neurotoxicity (P = .22)	GSH group had non-significantly higher tumor response rates and improved QoL scores, weight gain, neuroprotection, and nephroprotection versus the control group	5
Bogliun et al. ²⁵	Advanced ovarian cancer	n = 54 27 chemo + GSH 27 chemo alone	2500 mg/m ² , over 15 min, immediately before chemo	DDP 50 mg/m ² as iv infusion, in 26 pts; CDDP 75 mg/m ² , in 28 pts	CR + PR rates were 70% versus 59%; CR rates were 22% and 11%; no survival rates reported; no statistical analysis due to small sample size	26% versus 50% experienced neurotoxicity; 37% versus 78% experienced oliguria	GSH group had higher tumor response rates and less neurotoxicity and oliguria than the control group	1
Cascinu et al. ²⁷	Advanced gastric carcinoma	n = 50 25 chemo + GSH 25 chemo + placebo	1500 mg/kg i.v., over 15 min, immediately before chemo	DDP 40 mg/m ² , 5FU 500 mg/m ² , as i.v. infusion + epidoxorubicin, i.v. bolus, 9 weekly treatments	CR + PR rates were 76% versus 52%; CR rates were 20% and 12%; survival rates were 14 versus 10 months	17% versus 89% experienced neurotoxicity (P = .0001); other toxicities were similar between the two groups	GSH group had higher tumor response rates and significantly less neurotoxicity than the control group	5
Colombo et al. ²⁸	Relapsed, advanced ovarian cancer	n = 33 16 chemo + GSH 17 chemo alone	2500 mg/m ² , over 15 min, immediately before chemo	DDP 50 mg/m ² , 9 weeks as iv infusion	CR + PR rates were 75% versus 60%; CR rates were 44% and 27%; survival rates were 21 versus 15.9 months	13% versus 27% experienced neurotoxicity; other toxicities were similar between the two groups	GSH group had higher tumor response rates and less neurotoxicity than the control group	2
Fujimoto et al. ³¹	Operable gastric cancer (Stages I-IV)	n = 207 103 chemo + GSH 99 chemo alone	30 mg/kg i.v., from 10th postoperative day until discharge, with phenobarbital, 2 mg/kg	Mitomycin-C, 0.4 mg/kg and 0.2 mg/kg on days 1 and 2 of surgery; then 16 mg/kg Futrafal (FT-207, a 5-FU prodrug)	Survival rates were similar between the two groups as stated in text; no tumor responses reported	No significant difference in GI toxicities, higher serum 5-FU levels were noted in the GSH-treated group	GSH group had significantly higher survival rates at 3, 4, and 5 years (P < .025) for Stage III patients (n = 72)	1

Note on GSH administration: Pharmacokinetic studies indicate that GSH should be administered intravenously in the period that ranges from 30 min (and ideally 15 min) prior to and simultaneously with CDDP-based with chemotherapy. Cytoprotection has been shown by a GSH-CDDP ratio of 30:1 without interfering with chemotherapeutic activity.³²

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; G, gastrointestinal cancers; CDDP, cisplatin; VP-16, etoposide; 5-FU, fluorouracil, CR, complete response (or complete remission); PR, partial response; NS, not statistically significant. Not all toxicity data are reported, please refer to the text.

Table 2 Randomized clinical trials with melatonin (MLT) and chemotherapy

Reference	Tumor type(s)	No. of pts	MLT protocol	Chemotherapy regimen	Responses in MLT group versus Control group	Toxicity mitigation in MLT group versus Control group	Conclusion	Jadad Score
Lissoni et al. ³⁴	Advanced NSCLC	n = 100 50 chemo + MLT 50 chemo alone	20 mg orally in the evening	CDDP 20 mg/m ² as iv infusion for 3 days; etoposide 100 mg/m ² /day iv for 3 days	CR + PR rates were 35% versus 18% (P < .05); CR rates were 4% versus 0%; no control pts alive after 2 yrs, while 6% in the MLT group were alive after 5 years (P < .001)	18% versus 41% experienced neurotoxicity (P < .01); 14% versus 20% experienced thrombocytopenia (P < .01); 6% versus 41% experienced weight loss >10% (P < .001); 8% versus 35% experienced asthenia (P < .005)	MLT group had significantly improved tumor response and survival rates and significantly reduced toxicities versus control group	1
Cerea et al. ³²	Metastatic colorectal cancer	n = 30 14 chemo + MLT 16 chemo alone	20 mg orally in the evening	CPT-11 was given i.v. at 125 mg/m ² per wk for 9 consecutive wks	CR + PR rates were 36% versus 13% (NS); neither group reported a CR; survival rates not reported	29% versus 38% experienced diarrhea grades 3–4, resulting in a 50% dose reduction (NS)	MLT group had significant disease control versus the control group (86% versus 44%, P < .05); toxicities were reduced in MLT group, but not statistically significant	2
Lissoni et al. ³³	Advanced NSCLC Breast cancer GI tumors HNC	n = 250 104 NSCLC; 77 breast ca; 42 GI tract cancer; 27 HNC	20 mg orally in the evening	NSCLC: CDDP + VP-16 or GEM alone Breast cancer: DOX or mitoxantrone or paclitaxel alone GI tumors: 5FU, FA HNC: 5FU + CDDP	CR + PR rates were 34% versus 15% (P < .001); CR rates were 5% and 0% (P < .02); 1-yr survival rates were 51% versus 23% (P < .001)	20% versus 43% experienced myelosuppression (P < .001); 2% versus 13% experienced neurotoxicity (P < .05); 2% versus 10% experienced cardiotoxicity (P < .02); 10% versus 30% experienced stomatitis (P < .02); 27% versus 63% experienced asthenia (P < .001)	MLT group had significantly improved tumor response and survival rates versus control group; MLT group had significantly reduced toxicities versus control group	3
Lissoni et al. ³⁵	Advanced NSCLC	n = 70 34 chemo + MLT 36 chemo alone	20 mg orally in the evening	CDDP 20 mg/m ² as iv infusion for 3 days; etoposide 100 mg/m ² /day iv for 3 days	CR + PR rates were 32% versus 17% (NS); CR rates were 3% versus 0%; 1-yr survival rates were 44% versus 19% (P < .05)	12% versus 36% experienced myelosuppression (P < .05); 0% versus 14% experienced neuropathy (P < .05); 9% versus 33% experienced asthenia (P < .01); and 0% versus 44% experienced weight loss >10% (P < .001)	MLT group had significantly higher 1-yr survival rates versus control group; MLT group had significantly reduced toxicities versus control group	1

CR, complete response (or complete remission); PR, partial response; NS, not statistically significant 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.

Anticancer drugs: CDDP, cisplatin; VP-16, etoposide; GEM, gemcitabine; DOX, doxorubicin; 5FU, fluorouracil; FA, folinic acid (leucovorin); irinotecan, CPT-11; TAM, tamoxifen.

Not all toxicity data are reported, please refer to the text.

Table 3 Randomized clinical trials with various antioxidants and antioxidant combinations

Reference	Tumor type(s)	No. of pts	Antioxidant protocol	Chemotherapy regimen	Responses in Antioxidant versus Control group	Toxicity mitigation in Antioxidant group versus Control	Conclusion	Jadad Score
Pathak et al. ³⁹	Advanced NSCLC (Stages IIIb and IV)	n = 136 64 chemo + mixed antioxidants versus 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 as 3-h infusion on day 1) and carboplatin (dosage based on most recent creatinine clearance value before each chemo cycle)	CR + PR rates were 37% versus 33% (P = .28); CR rates were 3% versus 0%; 1 yr survival rates were 39% versus 33%; 2 yr survival rates were 16% versus 11% (P = .20)	No statistical difference in toxicities between antioxidant and control groups	No statistically significant difference in response or survival rates between groups, however, antioxidant group had non-significant advantage in both; antioxidants did not reduce toxicities	2
Falsaperla et al. ⁴²	Hormone-refractory prostate cancer (chemo naïve)	n = 48 consecutive pts 24 chemo + Ellagic acid versus 24 chemo alone	Ellagic acid, 180 mg (60 mg every 8 h) taken orally before meals during and between chemo cycles	Vinorelbine (25 mg/m ² , weekly for 6 wks) and estramustine (280 mg, 3×/day, for 42 days)	CR + PR rates were 58% versus 25%; CR rates were 25% versus 0% (NS); 2-year survival rates were 75% versus 58% (NS)	33% versus 75% experienced neutropenia (P < .05). Data also showed non-statistically significant decrease in anemia, nausea, anorexia, diarrhea, and neuropathy in antioxidant group	Ellagic acid group had higher tumor response and 2-yr survival rates; Ellagic acid group had significantly decreased neutropenia as well as non-statistically significant reductions in other toxicities	2
Weijl et al. ⁴⁰	Various malignant tumors: testicular (16), osteo-sarcoma (13), GI (6), urogenital (5), H& N (5), melanoma (3)	n = 48 pts 25 chemo + antioxidants versus 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 in varying dose intensities (highest planned dose: 100 mg/m ²) Each cycle 1–5 days of cytostatic drug infusions repeated every 21 days	CR + PR rates were 44% versus 48%; CR rates were 36% versus 26%; survival rates were not reported	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	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); more pts in antioxidant arm were able to receive optimal doses of CDDP	4
Pace et al. ⁴¹	Various malignant tumors: lung (15), HNC (5), ovarian (3), urethral (2), gastric (1), testicular (1)	n = 27 13 chemo + vitamin E versus 14 chemo alone	Vitamin E (300 mg/d, alpha-tocopherol) orally before chemo; then continued 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 on day 1 and GEM 1000 mg/m ² on day 1 and day 8 every 3 weeks	CR + PR rates were 62% versus 73% (NS); CR rates and survival rates were not reported	30.7% versus 85.7% experienced neurotoxicity (P < .01); other toxicities were similar between the two groups	Control group had higher tumor response rate than vitamin E group; Vitamin E group had a significant reduction in severity and incidence of neurotoxicity	2

Goel et al. ³⁸	Advanced breast cancer (Stages IIIB and IV)	n = 30 15 chemo + oral vitamin C versus 15 chemo alone	Ascorbic acid, 10 g/day, in two divided oral doses, throughout the chemo treatment period	Cyclophosphamide (600 mg/m ²), methotrexate (40 mg/m ²), and 5-FU (600 mg/m ²), on day 1 and day 8 of each 28-day cycle	CR + PR rates were 60% versus 33%; neither group reported a CR; survival rates were not reported	Toxicity differences not reported	Ascorbic acid group had higher tumor response rates versus control group; both groups had significant reduction of lump size P = .0003 for ascorbic acid and P = .03 for control	2
Meyskens et al. ⁴⁵	CML in chronic phase (persistent leukocytosis of at least 30,000 mm ³ found on at least two occasions)	n = 124 57 chemo + vitamin A versus 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)	No tumor response rates were reported; 5-yr survival: 48% versus 30%; after adjustment for survival-related factors	23% versus 4% experienced more grade 2+ toxicities (P = .002)	Vitamin A had higher 5-yr survival rates versus control group; 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 versus vitamin A supplemented patients	2
Israel et al. ⁴⁶	Metastatic breast cancer	n = 100 50 chemo + vitamin A versus 50 chemo alone	Vitamin A (350,000–500,000 IU/day, according to body weight)	Cyclophosphamide, bleomycin, doxorubicin and 5-FU, in varying treatment doses and schedules	CR + PR rates were 77% versus 67%; CR rates were 38% versus 15% (P < .02); projected 43 mo survival for responders: 93% versus 30% (P < .02)	No comparative toxicity analysis was undertaken	Vitamin A group had significantly improved tumor response and survival rates versus control group; postmenopausal women survival rates at 43 mo 78% versus 19% (P < .02)	1
Myers et al. ³⁶	Various malignant tumors: breast, lymphoma, soft-tissue sarcoma	n = 24 12 chemo + NAC versus 12 chemo alone	NAC, oral, 5.5 gm/m ² prior to each chemo treatment	Doxorubicin, 75 mg/m ² i.v. every 4 wks	CR + PR rates were 17% versus 7%; CR rates were 4% versus 0%; no survival rates were reported; no statistical analysis was conducted due to diversity of tumor types	NAC group experienced slightly more toxicities (nausea, alopecia, diarrhea, leucopenia) versus control group	NAC group had higher tumor response rates versus control group; NAC group experienced slightly more toxicities versus control group	2

CR, complete response (or complete remission); SD, stable disease; PR, partial response; NS, non-significant.
 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 are reported, please refer to the text.

studies, although antioxidants were administered, they were not administered concurrently with chemotherapy (245), or the antioxidant administered was synthetic (43). Synthetic antioxidants were not included in this study due to their inclusion in previous reviews.^{23,24} Twenty-eight of the studies met other inclusion criteria but did not report survival or treatment response data in the results. Also, five studies met the inclusion criteria, but were preliminary reports of studies that are included in the review. All studies were evaluated according to the Jadad scoring method. Results are provided in Tables 1–3.

The majority of the articles reported the use of glutathione (GSH) with chemotherapy (7) (see Table 1). Melatonin (MLT) was administered in four of the studies, three of which were from the same group in Italy (see Table 2). Two studies included vitamin A, two looked at a mix of antioxidants (vitamins C and E and selenium) and (vitamins C and E and beta-carotene). Only one study was included for each of the following: vitamin C, vitamin E, *N*-acetylcysteine, and ellagic acid (see Table 3).

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

Summary of studies

Glutathione and chemotherapy. Of the studies that evaluated glutathione given with chemotherapy intravenously, six of the seven trials combined glutathione with platinum-based drugs to treat a variety of cancer types (Table 1).^{25–30} All trials were performed in subjects with advanced or relapsed disease. Due to the known dose-limiting toxicities of platinum-based chemotherapy (neuropathy, ototoxicity, myelosuppression), the primary objective of these studies was to evaluate GSH for its neuroprotective effects. Reduced toxicities for patients undergoing chemotherapy often allow for a higher quality of life, less dose-reduction and completion of full chemotherapy regimens. In a larger study by Smyth et al.,³⁰ 58% of patients taking GSH were able to receive the full six cycles of chemotherapy, versus only 39% of the placebo group ($P = .04$). Specifically, significantly fewer patients in the GSH group experienced nephrotoxicity that kept them from receiving six cycles of treatment (11) than the control group (26) ($P = .012$).

Of six studies that reported on neurotoxicity, all of them observed similar²⁹ or greater^{25–28,30} reductions in neurotoxicity for the GSH group versus the control group, and two showed statistically significant reductions.^{26,27} Both significant reductions were reported by Cascinu et al. in two separate studies. In one study with 50 patients, a significant difference in the occurrence of neurotoxicity was seen between patients on GSH (17%) and the control group (89%) ($P = .0001$).²⁷ In another study with 52 patients, 26% of the control group experienced grade three or four neurotoxicity, while none (0%) of the GSH group experienced grade three or four neurotoxicity ($P = .01$).²⁶

Survival and/or treatment response data were also provided by the studies. For the six studies that reported overall response rates (complete response + partial response), none reported significantly lower response or survival in

antioxidant supplemented groups versus control groups (one study did not report any statistical analysis).^{25–30} One study reported a significant advantage in complete response rates for patients taking GSH within a subgroup of patients (24) who were surgically restaged.³⁰ Based on 'pathological' response, the GSH group reported a complete response in six of 13 patients versus only one of 11 patients in the control group ($P = .014$). In a study by Colombo et al.,²⁸ a non-significant advantage was shown by GSH supplemented patients who had both higher overall response rates than those patients receiving placebo (75% versus 60%, respectively), as well as higher complete response rates (44% versus 27%, respectively). Of note is that the GSH group achieved a superior response rate despite having a larger average tumor burden.

Only one study compared the effects of a non-platinum-based chemotherapy (mitomycin C and FT-207 (a 5-FU pro-drug)) plus placebo with chemotherapy plus supplementation of both phenobarbital and GSH.³¹ While the overall results were essentially the same between the two groups (only a slightly better treatment response was seen in the GSH supplemented group), when patients were grouped by gastric cancer stages, stage III patients had statistically significant higher survival rates for years 3–5 than the control group; the finding of statistical significance in this subgroup may have been more likely due to a larger number of subjects ($n = 72$ versus $n = 38, 48$ and 44 in other stages).

Melatonin and chemotherapy. Of four studies that compared melatonin supplementation to placebo, all reported better overall outcomes in those patients taking MLT than those taking placebo (Table 2).^{32–35} Three of the studies were conducted by Lissoni et al.^{33–35} and reported statistically significant increases in survival rates for those taking melatonin supplements. Response rates were also significantly higher in patients taking melatonin in two of the three Lissoni studies (35% versus 18%, $P < 0.05$ and 34% versus 15%, $P < .001$).^{33,34} Additionally, the number of patients with progressive disease was significantly lower in the MLT group than in the control group (12% versus 39%, $P < .01$).³⁴ In the study by Cerea et al.,³² no survival rates were reported, however, disease stabilization rates (partial response plus stable disease) were significantly higher in patients taking MLT than those taking placebo (86% versus 44%, $P < .05$). 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.

***N*-acetylcysteine (NAC) and chemotherapy.** Only one study that evaluated NAC with chemotherapy met the inclusion criteria (Table 3). Myers et al. evaluated the potential cardioprotective effect of adjuvant NAC on 24 patients who had failed to respond to their previous chemotherapy regimens.³⁶ While no cardioprotective effect was seen, 50% of the NAC-supplemented patients had stable disease or partial remissions versus 33% of the placebo group. However, no statistical analysis of these results was performed due to the diverse tumor types involved. Further, the small number of patients and the advanced disease stage limits the strength of this conclusion.

Vitamin C, mixed supplements, and chemotherapy. While the value of vitamin C as a potential cancer treatment has been debated for decades,³⁷ only one RCT was found that evaluated vitamin C treatment concurrently with che-

motherapy and reported on outcomes (Table 3).³⁸ In this study, a non-significant advantage was shown in objective response (complete response + partial response), which was higher in the vitamin C supplemented group (60%) than the placebo arm (33%). Additionally, while both the vitamin C group and the control group had significant reductions in the sizes of the average lump diameter before and after treatment, the mean change was $3.53 \pm .73$ in the vitamin C group versus $1.93 \pm .77$ in the control group.

Two recently published studies^{39,40} have included vitamin C as part of an antioxidant mixture given concurrently with chemotherapy. Pathak et al. evaluated vitamins C, E and beta carotene,³⁹ while Weijl et al. evaluated vitamins C, E and selenium.⁴⁰ Weijl reported poor adherence to the supplemental regimen: 46% of all patients did not drink the beverage (placebo or antioxidant) throughout the entire study. While the overall response rates were similar between the two groups (48% antioxidant group versus 44% control group), nine patients had a complete response in the antioxidant group, versus six patients in the placebo arm. A statistically significant correlation regarding improvement in toxicities was found between patients with the highest serum levels of the antioxidant supplements and the lowest loss of high-tone hearing after three cycles of chemotherapy ($P = .019$).

In the study by Pathak et al., while none of the results achieved statistical significance, an advantage in overall response rates (37% versus 33%) and median survival (11 months versus 9 months) was seen for patients taking the antioxidant supplements.

Vitamin E and chemotherapy. Pace et al. evaluated oral vitamin E supplements for a neuroprotective effect when combined with platinum-based chemotherapy (Table 3).⁴¹ A significant difference was seen between the incidence of neurotoxicity in the vitamin E supplemented group (31%) versus the placebo arm (86%) ($P < .01$). While not statistically significant, objective response (complete response plus partial response) was higher in the placebo group (73%) than in the supplemented patients (62%).

Ellagic acid and chemotherapy. Falsaperla et al. found prostate cancer patients taking ellagic acid had significantly decreased neutropenia over patients taking a placebo (33% versus 75%, $P < .05$) (Table 3).⁴² The ellagic acid group also showed slight, non-significantly higher survival times (ellagic acid group 5.85 months versus placebo 4.55 months), more complete responses (25% versus 0%), and greater reductions in serum PSA levels (>75% reduction: 58.3% versus 33.3%) than the control group in this high-risk subject population.

Vitamin A and chemotherapy. Two studies evaluated supplementation with vitamin A, a weaker antioxidant,^{43,44} Meyskens et al.⁴⁵ and Israel et al. (Table 3).⁴⁶ Israel et al. observed that patients supplemented with vitamin A showed a greater than twofold increase in the complete response rate (38% versus 15% for controls, $P < .02$). Among chemotherapy responders in both groups, the projected 43-month survival rate, based on a life table analysis using the Kaplan–Meier method and logrank test, was 93% in vitamin A-supplemented responders versus 30% in non-supplemented responders ($P < .02$). Classification of patients by menopausal status indicated that serum retinol levels were significantly elevated only in postmenopausal patients

supplemented with vitamin A ($P < .001$). For this subgroup, the response rates, duration of response and projected survival were significantly elevated. Postmenopausal patients on vitamin A ($n = 25$) had a 78% chance of surviving 43 months, compared to 19% for non-supplemented ($n = 30$) postmenopausal women ($P < .02$).

In the study by Meyskens et al., patients in the control group experienced less grade 2 + toxicities (4%) than the vitamin A group (23%) ($P = .002$). This was the only study to report a statistically significant reduction of toxicity in the control group versus the antioxidant group, which was not unexpected for vitamin A supplementation. Patients in the vitamin A group had longer durations of clinical progression-free survival (median 46 months) and overall survival (51 months) compared to those in the chemotherapy-alone group (38 and 44 months, respectively); however, the differences were not statistically significant.

Discussion

Overview of outcomes

From the 19 studies included in this review, no evidence was found that supported concerns that antioxidant supplementation given concurrently with ROS-generating chemotherapy diminished the efficacy of the chemotherapy in study populations comprising mostly advanced or relapsed patients. In contrast, 17 of the 19 RCTs included in this review showed either a statistically significant advantage or non-significantly higher survival and/or treatment response in those patients given antioxidants. Specifically, of 13 reports on survival, all showed similar^{26,29–31,39} or better^{27,28,33–35,42,45,46} (four being statistically significant^{33–35,46}) survival rates for the antioxidant group over the control group. Additionally, while one study reported similar survival results between the antioxidant arm and control overall, the largest subgroup (stage III patients taking antioxidants) was found to have a statistically significant survival advantage compared to the control group.³¹

For the 17 studies that reported overall response, 16 reported similar^{26,29,39,40} or better^{25,27,28,30,32–36,38,42,46} overall response rates for the antioxidant supplemented group (two being statistically significant^{33,34}) than the control group. Of 15 studies that reported complete response rates, all reported similar^{26,29,32,34–36,38,39} or better^{25,27,28,33,40,42,46} (two being statistically significant^{33,46}) response rates for the antioxidant supplemented group than the control group. One study reported complete response rates for a subgroup (surgically restaged patients taking antioxidants) that responded significantly better than the control group (46% versus 9%, $P = .014$).³⁰ No studies reported significantly worse survival or response in the antioxidant supplement group.

Toxicities were also improved by antioxidant supplementation. Of 17 studies that reported general toxicities (non-neurological toxicities), 15 showed similar^{26–28,31,39–41} or reduced^{25,29,30,32–35,42} toxicities (three of which were statistically significant^{33–35}) in the antioxidant group when compared with the control group. Only one study reported significantly greater general toxicity in the antioxidant group than the control,⁴⁵ although these results were not

surprising due to the well documented toxicities of high-dose vitamin A.¹⁷ In another study, two of eight toxicities measured were non-significantly higher, however, these results were difficult to interpret due to non-adherence within the antioxidant group.³⁶ Eleven studies reported specifically on neurotoxicity and all¹¹ showed the antioxidant supplement group experienced similar²⁹ or less neurotoxicity^{25–28,30,33–35,41,42} (six being statistically significant^{26,27,33–35,41}) than the control group. The variety of outcome measures and cancers treated in the studies reviewed do not allow final conclusions on the question of tumor protection by antioxidants, and this question remains open. Interactions with other agents are also possible; for instance, one clinical study not included in this review found that a combination of vitamin E and the antihypertensive nifedipine decreased acute cardiac toxicity, but increased the clearance of doxorubicin.⁴⁷ Synthetic antioxidants such as amifostine, used concurrently with chemotherapy to reduce side effects have yet to demonstrate interference with chemotherapeutic efficacy, though the potential for interference remains somewhat controversial.⁴⁸

While all of the regimens in the studies in this review included at least one drug of a class thought to produce higher levels of oxidative stress (e.g. anthracyclines, platinum coordination complexes), there is some indication that free-radical induced damage may not be the only mechanism of action of these drugs.⁴⁹ Thus, while antioxidants may have reduced free-radical damage to normal tissues leading to diminished toxicity, the non-oxidative cytotoxic mechanisms of the drugs may remain unaffected by antioxidant supplementation. Further, the significant reductions in toxicity may alleviate dose-limiting toxicities to such an extent that more patients successfully complete prescribed regimens. Three studies reviewed reported that antioxidant groups experienced better treatment tolerance in terms of less dose-reduction and higher rates of completing full chemotherapy regimens than control groups.^{28,30,32}

Study limitations

The 19 RCTs summarized in this review encompassed diverse populations of cancer patients in terms of tumor and treatment type. The studies should generally be regarded as Phase II studies because of their small size, and are thus most suitable for obtaining treatment response data. Presentation of survival data may be considered somewhat premature, though nevertheless intriguing. To reliably assess modest yet clinically important treatment effects, trials with substantially larger sample sizes would be necessary. Some studies identified in this review may have been designed and powered to detect differences in toxicity rather than in treatment response or survival. Lack of adequate statistical power to detect differences in survival or response would render those studies showing similar or non-significantly better results in the antioxidant arms difficult to interpret. However, in the absence of statistical power calculations (either a priori or post hoc), a common problem in most randomized trials, it is difficult to say whether clinically important effects may have been missed in the smaller trials.⁵⁰ Most of the subjects in the studies had advanced or relapsed disease; the applicability of these

results in patients with earlier, more chemosensitive disease is not addressed by these studies. Jadad scores for many of the studies were low; only four studies were found that included double-blinding in the procedure. Of the studies that did use double-blinding, three evaluated neurotoxicity, two of which reported a statistically significant reduction of neurotoxicity in the antioxidant supplemented groups.^{26,27,30,40} The response rates were similar to or non-significantly greater than those of control groups in all four studies.

Implications for clinical practice

This systematic review, the first to consider the impact of antioxidant supplementation in combination with chemotherapy, provides suggestive evidence that antioxidant supplementation helps reduce some adverse reactions including neurotoxicity, thrombocytopenia, diarrhea, thus enabling increased or uninterrupted dosing in patients who otherwise may discontinue treatment due to side effects. The importance of reducing dose-limiting toxicities was shown recently by Neugut et al.⁵¹ In this study, colon cancer patients over age 65 who received a full five to seven months of chemotherapy had higher survival rates than those who only received one to four months of treatment. Furthermore, among the 30% of patients who dropped out of chemotherapy treatment early, mortality rates were twice those of the group who completed therapy.

While many of the trials summarized in this review found survival and/or treatment response rates to be similar or higher in the antioxidant groups than placebo, the number of small, underpowered studies and diversity of tumor and treatment type limits any clear conclusions about potential additive effects of antioxidant supplementation during chemotherapy. However, this review did not detect diminished chemotherapeutic efficacy in patients receiving antioxidant supplementation in randomized trials. The lack of negative impact of antioxidant supplementation on efficacy of ROS-generating chemotherapy in the studies reviewed, and the potential to diminish dose-limiting toxicity suggest that the clinical application of antioxidant supplementation during chemotherapy should be further explored. Future research on concurrent use of antioxidants and chemotherapy should employ larger sample sizes and better research designs.

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