Table 8. Randomized clinical trials with glutathione, vitamin E, various antioxidants, and antioxidant combinations and chemotherapy (selection) [32]

Trial/tumor type(s) [Ref.]	Patients, n	Treatment protocol	Chemotherapy regimen	Toxicity mitigation in treatment group vs. control group	Responses in treatment group vs. control group	Conclusion
Glutathione (GSH)						
Advanced colorectal cancer [58]	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 5-FU, 1,500 mg/m^2 as IV 24-h infusion with leucovorin, 150 mg/m^2 as infusion	30 vs. 100% in GSH vs. control group 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 group; neither group reported a CR; median survival: 16 vs. 17 months	GSH group experienced significantly reduced neuropathy vs. control group
Advanced ovarian cancer [59]	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 patients; CDDP 75 mg/m^2 given IV in 28 patients	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 control group
Gastric cancer [60]	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 months	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
Vitamine E						
Solid or non-myeloid malignancy [66]	n = 32	300 mg/2× 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 in 3/16 (18.7%) vitamin E patients vs. 10/16 (62.5%) in control (p = 0.03). PNP score vitamin E 2.25 vs. control 11 (p = 0.01)	n/a	vitamin E protects from peripheral nerve damage
Various malignant tumors (n): lung (15), HNC (5), ovarian (3), urethral (2), gastric (1), testicular (1) [30]	n = 27, 13 chemo + vitamin E vs. 14 chemo alone	300 mg/day, 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 IV on day 1 and GEM 1,000 mg/m^{2}IV on days 1 and 8 every 3 weeks	30.7 vs. 85.7% experienced neurotoxicity (p < 0.01); other toxicities were similar between the 2 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
Solid or nonmyeloid malignancy [61]	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%) vitamin E patients vs. 11/16 (68.5%) control; p = 0.026	n/a	vitamin E may have important neuroprotective effects

Table 8 (continued)

Trial/tumor type(s) [Ref.]	Patients, n	Treatment protocol	Chemotherapy regimen	Toxicity mitigation in treatment group vs. control group	Responses in treatment group vs. control group	Conclusion
Antioxidants						
Various malignant tumors (n): testicular (16), osteo-sarcoma (13), GI (6), urogenital (5), HNC (5), melanoma (3) [62]	n = 48; 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 patients 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 patients in antioxidant arm were able to receive optimal doses of CDDP; response rates were similar between the 2 groups, however, CR rates were higher in antioxidant group than control group
Children with leukemia or non-Hodgkin's lymphoma [63]	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
Ovarian cancer [64]	n = 62	selenium (200 µg/day) for study group in addition to orally taken mix of β-carotene, vitamin C, vitamin E, vitamin B2, vitamin B3, for both	100 mg/m^2 IV CDDP and 600 mg/m^2 IV cyclophosphamide	significant increase in WBC in selenium group ($p < 0.001$); significant decrease in all side effects, except diarrhea	n/a	beneficial effects of selenium found when taken with chemo
Cancer of digestive tract [65]	n = 60	oral selenium (200 µg/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 patients malnourished at baseline. 21/30 (70%) selenium group showed no further decline but increase in appetite; 24/30 (80%) control had significant decline of all parameters (body weight, etc.) ($p < 0.01$)	n/a	selenium plus zinc may improve general clinical course

chemo = Chemotherapy; IV = intravenously; CR = complete response (or complete remission); SD = stable disease; PR = partial response; NS = non-significant; n/a = not applicable; AUC = area under the curve; PPN = peripheral neuropathy score; NSCLC = non-small cell lung cancer; HNC = head and neck cancers; GI = gastrointestinal cancers; CML = chronic myelogenous leukemia; CDDP = cisplatin; VP-16 = etoposide; GEM = gemcitabine; DOX = doxorubicin; 5-FU = fluorouracil; FA = folinic acid (leucovorin); irinotecan = CPT-11; TAM = tamoxifen; MTX = methotrexate; Co-Q10 = coenzyme Q12.