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Systematic Review: Generating Evidence-Based Guidelines on the Concurrent Use of Dietary Antioxidants and Chemotherapy or Radiotherapy

Akiko Nakayama^{1,*}, Karen P. Alladin^{2,*}, Obianuju Igbokwe², and Jeffrey D. White²

¹Preferred Staffing Group, Inc., Washington, District of Columbia, USA

²Office of Cancer Complementary and Alternative Medicine, National Cancer Institute, Bethesda, Maryland, USA

Abstract

The risk–benefit ratio for concurrent use of dietary antioxidants with chemotherapy or radiation therapy is a controversial topic. In this review, the medical literature on concurrent antioxidant use with chemotherapy or radiotherapy was assessed and further steps for generating evidence-based guidelines are suggested. The clinical cancer research community should cooperate and focus new studies on the use of a specific combination of antioxidant and chemotherapy or radiotherapy, and determine optimal doses for a specific cancer setting. Mechanistic studies on the interaction between antioxidants and conventional cancer therapy could lead to novel biomarkers for assessing dose adequacy.

Keywords

Treatment; Supportive care and symptom control; Chemotherapy

INTRODUCTION

Recent studies show that an increasing number of Americans are seeking complementary and alternative medicine (CAM) (1, 2). Cancer patients are among those who are looking to CAM for more treatment options to improve their disease status as well as their quality of life. Many cancer patients use dietary supplements with antioxidants during or after conventional cancer treatment attempting to enhance the benefits of treatment, prevent or palliate side effects, or maintain or improve general health and well-being (3–5). Cancer patients continue to do this regardless of a relative lack of high-level evidence of antioxidant's safety, efficacy, or benefit when combined with conventional cancer therapies. Antioxidants are widely viewed by patients as a safe, healthy means to protect cells and tissues from damage caused by free radicals, thus providing a preventive measure against the onset of cancer and side effects of chemotherapy and radiation therapy. Antioxidants act to quench free radicals or prevent the formation of free radicals. Free radicals are highly reactive chemicals with incomplete electron shells, making them chemically volatile and prone to taking electrons from other molecules (e.g., lipids and nucleotides), which can lead

Correspondence to: Jeffrey D. White, MD, National Cancer Institute, Office of Cancer Complementary and Alternative Medicine, 6116 Executive Boulevard, Suite 609, Bethesda, MD 20892, USA. jeffreyw@mail.nih.gov.

*Akiko Nakayama and Karen P. Alladin contributed equally to this work.

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to damage of cell membranes or DNA. Dietary antioxidants take part in cellular redox reactions and can act as either antioxidants (electron donors) or prooxidants (electron acceptors), depending on the physiological environment, their concentration, and general oxidative state (6).

There are conflicting arguments regarding the use of antioxidant supplements while a cancer patient is undergoing conventional treatment. One position is that antioxidants help protect and repair healthy cells that are damaged by chemotherapy or radiation therapy, which can result in fewer or less severe side effects. Proponents of this argument also assert the ability of antioxidants to directly induce apoptosis in malignant cells and to enhance antitumor effects of chemotherapy *in vitro* and *in vivo* (7–10). Opponents are concerned that antioxidants directly oppose the mechanisms of conventional cancer treatment, working to repair and protect cells by lowering oxidative damage, while many cancer treatments aim to destroy cancer cells by causing oxidative damage (11, 12).

Many published studies have reported the effects of antioxidants as an adjuvant therapy for cancer patients while undergoing conventional cancer therapy. Recent reviews have come to divergent opinions about the appropriateness of recommendations to patients for (9, 10) or against (13, 14) the concurrent use of antioxidants with either chemotherapy or radiation therapy. Although questions about the risk–benefit ratio have apparently been adequately answered for some, intriguing results from various studies have prompted many to call for more research (13, 15–18).

We conducted a systematic review of the published clinical trials examining the effects of dietary antioxidants taken concurrently with chemotherapy or radiation therapy in an attempt to (a) characterize the research and clinical questions under investigation in these studies, (b) determine what further research would be necessary to strengthen efforts at clinical guidelines development, and (c) identify areas of promise for future research.

MATERIALS AND METHODS

Relevant articles were obtained through literature searches of MEDLINE via PubMed, EMBASE, and the Cochrane Library. These databases were searched for published clinical trials examining the use of antioxidant supplements as an adjuvant therapy to conventional chemotherapy and/or radiotherapy. The existing files regarding antioxidants at the National Cancer Institute (NCI)'s Office of Cancer CAM (OCCAM) were surveyed for this review as well. Additional articles found in the bibliographies of retrieved articles were added.

We included only antioxidants that are dietary compounds, though they may have been administered parenterally. Only studies examining the effects of antioxidant supplementation used concurrently with conventional therapy were included. Studies investigating the chemopreventive effects of antioxidants were excluded. Articles about certain compounds with antioxidant activity but with other known prominent and potentially therapeutic mechanisms of action, such as retinoids, isoflavones, and melatonin, were excluded (19–21). Limits for clinical trials and English language were used, but no limit was placed on the publication years.

RESULTS

Fifty-two clinical trials, which investigated the concurrent use of diet-derived antioxidants with chemotherapy and/or radiotherapy, were found. Among them, 26 clinical trials used glutathione or reduced glutathione (GSH) (22–47), 11 used a type of vitamin E such as α -tocopherol or dl- α -tocopherol acetate (48–59), 5 used *N*-acetylcysteine (NAC; 60–64), and others ($n = 10$) used vitamin C, selenium, coenzyme Q10, zinc, or a combination of

antioxidants (65–74; Table 1). Since GSH, vitamin E, and NAC were studied most frequently, we further analyzed the reports that examined these antioxidant supplements.

GSH

The combination of GSH and chemotherapy or radiation therapy is the most studied category in our results (26 of 52 studies). We analyzed study type, definition of antioxidant used, supplier name, cancer type, rationale for choosing a specific antioxidant dose, rationale for choosing the specific antioxidant, and conventional cancer therapy combination, as well as the primary endpoints of the studies (Table 2). The majority study type was single arm (65%) followed by randomized controlled trials (RCTs) (20%), and double-blind, placebo-controlled, randomized trials (15%). The antioxidant substances were described as either “glutathione” (69%) or “reduced glutathione” (31%). Only 38% of the studies identified the product or supplier name. Ovarian cancer (42%) was the most studied cancer type.

We found no dose-finding study to determine the optimal dose of GSH. Regarding dose selection, six studies (23%) mentioned the rationale for selecting the GSH dose, with only one study (22) describing the rationale for determining the selected GSH regimen and dose while five studies (33, 38, 40, 43, 46) stated that they followed the dose of previous studies. The other 20 studies (77%) did not mention a justification for choosing their antioxidant dose. Consequently, the doses of GSH administered varied widely with fixed doses ranging from 1.2 to 5 g per administration and adjusted dosing ranging from 1.5 to 3 g/m². The most frequently adopted dose, 1.5 g/m², was used in some earlier studies (27, 43); however, these studies did not explain why this dose was selected. The timing of intravenously administered GSH at 15–30 min before chemotherapy or radiation therapy was commonly used due to its short half-life. The antioxidant used, its dose, conventional cancer therapy, cancer type, study type, and size of each study are listed in Table 3.

GSH was most frequently administered with cisplatin (CDDP)-based chemotherapy (88%, 23 of 26). Despite the frequent use of CDDP, due to the variance of GSH dose, only five studies (19%) used the same combination and dose on the same cancer (30, 31, 33–35). All of them were single-arm studies demonstrating that adding GSH to CDDP-based chemotherapy could improve tumor response in gastric cancer patients (compared to historical controls) with some also showing a neuroprotective effect.

We further divided all clinical trials based on whether tumor-related (TR) outcomes were assessed or symptom/side effect management or prevention (SM) endpoints. TR corresponds to objectively assessed tumor response or patient survival, whereas SM corresponds to the management and prevention of cancer symptoms or conventional cancer-therapy-induced side effects. Twelve trials (46%) assessed SM endpoints, mostly prevention of CDDP-induced neurotoxicity, seven studies (27%) assessed TR outcomes, and seven studies (27%) assessed both TR and SM outcomes (Table 2).

Among the four double-blind, placebo-controlled RCTs, two studied ovarian cancer patients (22, 23). In a trial of 151 ovarian cancer patients, Smyth *et al.* (22) found that 3 g/m² of glutathione administered immediately before CDDP helped more patients achieve six courses of CDDP (100 mg/m²; $p = .04$) (22). They also found significantly less nephrotoxicity, as measured by creatinine clearance ($p = .006$), as well as significantly better quality of life in the GSH treatment arm compared to the placebo arm. Parnis *et al.* found less toxicity among ovarian cancer patients who received CDDP and GSH compared with CDDP and placebo, though the difference was not statistically significant (23). In a colorectal cancer clinical trial with the same study type, Cascinu *et al.* found significantly reduced neuropathy in GSH arm versus placebo ($p = .003$), and no reduction in oxaliplatin

activity when concurrently administered with GSH (38). The double-blind, placebo-controlled RCT of patients with advanced gastric cancer found higher rates of tumor response and complete remission, and less neuropathy in the GSH treated arm ($p = .0001$; 32). All five RCTs using GSH showed better results in their primary endpoints in the GSH treatment arm, but none of them had statistical significance (24, 37, 39, 40, 43). In the 17 single-arm trials, 16 (94%) found that GSH treatment yielded better results in their primary endpoints than expected with the chemotherapy regimen alone (25–31, 33–36, 42, 44–47). The one single-arm study that did not find better results in the primary endpoint found no apparent interference in the therapeutic effect from adding reduced GSH to CDDP (41).

Vitamin E

The second most studied antioxidant category is vitamin E ($n = 11$). RCTs account for the majority (55%) of these studies, followed by double-blind, placebo-controlled RCTs (18%), non-RCTs (18%), and single-arm studies (9%; Table 2). The intervention was most frequently described as “ α -tocopherol” (45%), followed by “dl- α -tocopherol acetate” (18%), dl- α -tocopherol (9%), d- α -tocopherol (9%), tocopherol (9%), and vitamin E (9%). In seven studies (63%), the supplier or product name of the vitamin E was identified.

The doses of vitamin E varied from 200 mg to 3200 IU per day (Table 3). The vitamin E was administered orally in nine studies (82%), intramuscularly in one (58), and as an oral rinse in one (51). The great majority (82%) of the reports did not mention the rationale for the antioxidant dose. Doxorubicin-based chemotherapy (36%) and radiation therapy (36%) were most frequently used as conventional cancer therapy. However, only two studies used the same vitamin E and conventional cancer therapy combination on the same cancer type (52, 53). Assessment of chemotherapy or radiotherapy side effects was the primary endpoint in most of the trials (73%).

Head and neck cancer patients undergoing radiation therapy were the subjects in both of the double-blind, placebo-controlled RCTs of vitamin E (51, 56, 57). Ferreira *et al.* found significantly less mucositis in patients receiving α -tocopherol compared to those receiving placebo ($p = .038$; 51). In Bairati *et al.*'s trial, patients treated with dl- α -tocopherol had higher second primary cancer and recurrence rates during the supplementation period but lower rates after discontinuation of supplements (56). They also found less acute adverse effect of radiotherapy in the supplementation group than those receiving placebo (i.e., radiotherapy only; 57).

Two RCTs using α -tocopherol and CDDP-based chemotherapy found significantly lower neurotoxicity in the supplement arm than control (48, 49). In two other RCTs, Misirlioglu *et al.* found that adding α -tocopherol and pentoxifylline could significantly reduce radiation-induced lung toxicity and enhance survival among lung cancer patients (52, 53). These were the only trials administering the same antioxidant regimen and dose combined with radiotherapy.

NAC

The third most studied antioxidant substance was NAC ($n = 5$). Study type varied from single-arm to placebo-controlled RCT, but no double-blind, placebo-controlled RCTs were found. All five studies identified the antioxidant as NAC. Three studies (60%) were in patients with lung cancer. Two studies (40%) stated the source of the antioxidant used (62, 64). All of the five studies used different NAC doses.

Two studies focused on the use of NAC to prevent treatment-related side effects. Both showed better results for the NAC treatment arm over the control arm in their primary endpoint, namely, neuropathy from oxaliplatin (60) and cardiomyopathy from doxorubicin

(61). The other three studies focused on tumor-outcome-related endpoints in lung cancer patients, and none showed any apparent benefit for the experimental arm (62–64).

DISCUSSION

The ability of physicians and patients to make confident assessments of the risk–benefit ratio of concomitant use of dietary antioxidants with conventional cancer therapies is limited by many factors including the presence of significant gaps in clinical trial results. Clinical trials examining the potential benefit of these combinations have been conducted since the late 1980s. However, despite many trials demonstrating positive effects of combined therapies, none of the combinations has yet gained widespread acceptance in clinical practice. Many of these trials were small and thus lack sufficient statistical power to provide robust answers. Meta-analyses have not been done and would be unlikely to provide more clarity for the reasons stated below.

Our investigation identified trials studying a diverse selection of antioxidants, including glutathione, vitamin E, NAC, vitamin C, selenium, coenzyme Q10, and zinc as well as some combinations. This variety of types of dietary antioxidants investigated in these studies contributes to a significant heterogeneity in the research and clinical questions asked.

Differences in formulations or descriptions of an antioxidant can also cause confusion in comparison between studies of, ostensibly, the same antioxidant. Perhaps, this is best illustrated with vitamin E, a term that can be used to refer to single isomers, racemic mixtures, or mixtures of any of several tocopherols (e.g., α -, β -, γ -, δ -tocopherols). Studies identified in this review reported using several different forms of tocopherols and one simply described the compound as “vitamin E.” When α -tocopherol was specified, often the specific salt was not. Preclinical research has demonstrated differences in the bioavailability of different stereoisomers of α -tocopherol and in biological activity of the acetate and succinate salts of α -tocopherol (75–79).

The dosage and schedule of administration for antioxidants of the same type often differed between the studies we reviewed. These studies generally did not provide a rationale for the dosage, formulation, or schedule used.

The selection and specifics of the conventional cancer therapy protocol also often differed between studies, as did the cancer type and stage. Among the 52 clinical trials we reviewed, only five studies of glutathione and two studies of NAC used exactly the same antioxidant and conventional cancer therapy doses and regimens in the same cancer types.

A search of Clinicaltrials.gov identified 38 ongoing trials of antioxidant and chemotherapy or radiotherapy combinations (80). Several steps are needed to optimize the chance for ongoing and future research endeavors to lead to a satisfactory evidence base for development of clinical practice guidelines of the concurrent use of dietary antioxidants and conventional cancer therapies. First, a community of interested researchers must come to consensus and focus efforts on one, or a small number of antioxidant and conventional cancer therapy combinations and specific clinical research questions. This has been accomplished to a limited degree with the combination of glutathione and cisplatin-based chemotherapy for treatment of gastric cancer (30, 31, 33–35). Initial efforts should focus on a rational approach to selection of the antioxidant and chemotherapy or radiotherapy partner. Both results from well-designed and conducted preclinical studies and findings from previous clinical trials can provide a basis for these choices.

Second, studies are needed that reveal the mechanism(s) of action of specific combinations of antioxidants and conventional cancer therapies. Several review articles and reports of

animal studies (81–83) have speculated about the mechanism of action for the combination of cisplatin and reduced glutathione, but the involved pathways remain unknown. The identification of biomarkers that reflect these mechanisms of action may also help guide clinical trial design (84, 85). Recent evidence pointing to differences in survival after treatment of patients associated with a polymorphism of the glutathione S-transferase gene may suggest possibilities for such useful markers (86).

Next, a concerted effort should be made to determine the optimal formulation, dose, and schedule of the antioxidant under investigation in combination with a specific chemotherapy regimen through appropriately designed, dose-escalation studies. In the early trials of glutathione, the dose of 1.5 g/m² was selected without determining an optimal dose, out of concern for possibly reducing the effectiveness of CDDP (43). While some subsequent studies adopted this dose, others used various doses, generally without providing a rationale in the final paper. We found no study that attempted to determine the optimal doses of an antioxidant–chemotherapy combination.

Finally, given these important inconsistencies between reports, we suggest that journals considering future articles on this topic require authors to adhere to a few basic criteria, which would improve future summary analyses on this topic (Figure 1).

An example from colorectal cancer therapy illustrates the successful accomplishment of some of these proposed steps. Folinic acid was found to significantly augment the therapeutic index of fluorouracil (5-FU) through meta-analysis of clinical trials and is currently accepted as a standard treatment (87). Folinic acid may not have gone through a full dose-finding process, but low and high doses were tested in at least one study (78).

Despite some encouraging findings regarding possible benefits of antioxidant and chemotherapy combinations, few comparative phase III studies have been done and none have demonstrated an effect of the magnitude of adding folinic acid to 5-FU (77). However, folinic acid increases the toxicity of 5-FU (88), whereas various antioxidants either diminish toxicity [e.g., glutathione and cisplatin (22, 32, 38)] or have no effect on toxicity [e.g., selenium and irinotecan (72)]. The mechanism of action by which folinic acid modulates the activity of fluorinated pyrimidines, such as 5-FU, has been well elucidated. Perhaps, the lack of understanding regarding the pathways involved in the cytoprotective and therapeutic augmentation effects of dietary antioxidants with specific cancer therapeutics may be one reason the combinations have not been more thoroughly studied.

The US NCI's Division of Cancer Treatment and Diagnosis has established some areas of special interest with regard to the development of its grant portfolio (89). One of these topics is the identification of complementary approaches that augment the therapeutic index of conventional anticancer therapeutics. Research proposals assessing the combined use of antioxidants and conventional cancer therapies would address this topic and thus would be eligible via either of two program announcements (90, 91).

A potential limitation of our review is selection bias. We only searched and included publications with their full text written in English, possibly overlooking some relevant clinical trials in non-English language journals. Although we only searched through MEDLINE via PubMed, EMBASE, and Cochrane Library, additional clinical trials from the bibliographies of retrieved articles and OCCAM's archives were added to get as complete a list as possible.

CONCLUSION

Clinical research exploring combinations of dietary antioxidants and chemotherapy or radiation therapy has seemingly focused on the demonstration of a detectable advantage, or disadvantage, over chemotherapy, or radiation therapy alone. Several published studies have provided individual results addressing these questions, but the resulting portfolio of findings is inadequate to allow the confident development of specific clinical guidelines of appropriate use either for the mitigation of therapy-related side effects or the augmentation of anticancer activity. A greater homogeneity of treatment protocols in the future and more thorough reporting of the antioxidant type and formulation used would produce results that could be used to determine if evidence-based recommendations for or against the use of specific combinations in specific clinical situations are warranted.

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Figure 1. Recommendations for reporting of clinical research with combinations of antioxidants and chemotherapy or radiotherapy.

Combinations of conventional cancer therapy and antioxidant supplement

Table 1

Treatment modality	Glutathione	Reduced glutathione	α -toc	dl- α -toc acetate	α -toc + β -car	vit. E or digoxin	NAC	vit C	vit C, vit E, NAC	dl- α -toc succinate, β -car, Vit C	Se	Se, β -car, vit C, E, B2, B3	Se, vit C, dl- α -toc acetate	Seleno-methionine	Co Q10	Zn
CDDP	22, 23, 24, 25	40, 41	48													
CDDP + CPA	26, 27, 28, 29	42, 43										69				
CDDP + 5-FU + 4epiDOX + 6S-LCV + G-CSF	30, 31, 32, 33, 34, 35															
CDDP + Carboplatin		44														
CDDP + Bleomycin	36															
CDDP + (etoposide or 5FU)	37															
CDDP + 5FU		45, 46														
CDDP-based			49										70, 71			
CPA		47														
Oxaliplatin + 6S-LCV + 5FU	38						60									
5FU + LCV			50													
DOX				54				61								
DOX + cytarabine + thioguanine					58	59										
DOX + FU + CPA				55												
Paclitaxel + carboplatin																
Anthracyclines											67				73	
Doxorubicin, Interferon, desferrioximine																
Ifosphamide							62, 63									
Irinotecan														72		
DOX $\pm$ RT									66							
RT	39		51		56, 57		64									74
RT + PTX			52, 53													

Note: Each cell contains the reference number(s). CDDP, cisplatin; CPA, cyclophosphamide; 5-FU, 5-fluorouracil; DOX, doxorubicin; LCV, leucovorin; RT, radiation therapy; PTX, pentoxifylline; GSH, glutathione; NAC, N-acetylcysteine; toc, tocopherol; vit, vitamin; β -car, β -carotene; Se, selenium; Co Q10, Coenzyme Q10; Zn, zinc.

Table 2

Study characteristics of clinical trials using GSH, vitamin E, and NAC

Categories	Type	GSH (<i>n</i> = 26)		Vit E (<i>n</i> = 11)		NAC (<i>n</i> = 5)		Overall (<i>n</i> = 42)	
		# of articles	% among GSH studies	# of articles	% among vit. E studies	# of articles	% among NAC studies	# of articles	% among all studies
Study type	Double-blind, placebo-controlled RCT	4	15	2	18			6	14
	Placebo-controlled RCT					1	20	1	2
Definition of antioxidant	RCT	5	20	6	55	1	20	12	29
	Nonrandomized, controlled trial			2	18	2	40	4	10
	Single arm	17	65	1	9	1	20	19	45
	Glutathione	18	69					18	43
Product or supplier name	Reduced glutathione	8	31					8	20
	α -tocopherol			5	46			5	12
	dl- α -tocopherol acetate			2	18			2	5
	dl- α -tocopherol			1	9			1	2
	d- α -tocopherol			1	9			1	2
	tocopherol			1	9			1	2
	vitamin E			1	9			1	2
	N-acetylcysteine					5	100	5	12
	Unstated	16	62	4	36	3	60	23	55
	Boehringer Mannheim	9	35					9	21
Cancer type	Roche			3	28			3	7
	Others	1	3	4	36	2	40	7	17
	Ovarian	11	42					11	26
	Gastric	6	23					6	14
	Colorectal	2	8					2	5
	Head and neck	2	8	2	18			4	9
	Breast			2	18			2	5
	Lung			2	18	3	60	5	12
	Others	5	19	5	46	2	40	12	29

Categories	Type	GSH (<i>n</i> = 26)			Vit E (<i>n</i> = 11)			NAC (<i>n</i> = 5)			Overall (<i>n</i> = 42)		
		# of articles	% among GSH studies	# of articles	% among vit. E studies	# of articles	% among vit. E studies	# of articles	% among NAC studies	# of articles	% among all studies	# of articles	% among all studies
Reason for choosing antioxidant dose	Unexplained	20	77	9	82	3	60	32	76				
	Previous clinical trials	5	19	2	18	1	20	8	20				
	Animal/mechanism studies					1	20	1	2				
	Both clinical trials and animal/mechanism studies	1	4					1	2				
Reason for choosing AO and CT/RT combination	Unexplained					1	20	1	2				
	Previous clinical trials	10	38	7	64			17	41				
	Animal/mechanism studies	3	12	3	27	2	40	8	19				
	Both clinical trials and animal/mechanism studies	13	50	1	9	2	40	16	38				
Primary endpoint	TR	7	27	2	18	2	40	11	26				
	SM	12	46	8	73	2	40	22	52				
	Both TR and SM	7	27	1	9	1	20	9	22				

RCT, randomized controlled trial; CT, chemotherapy; RT, radiation therapy; AO, antioxidant; GSH, glutathione; NAC, *N*-acetylcysteine; CDDP, cisplatin; 5-FU, 5-fluorouracil; LCV, leucovorin; CPA, cyclophosphamide; DOX, doxorubicin; IFX, ifosfamide; PTX, pentoxifylline; NSCLC, nonsmall cell lung cancer; SCLC, small-cell lung cancer; HNC, head and neck cancer; TR, treatment-related outcomes; SM, symptom/side effect management or prevention.

Table 3

Detailed analysis of clinical trials sorted by cancer types and publication dates

GSH								
Cancer type	Cancer type as stated in article	Reference	Pts #	Study type	AO	AO dose	CT or RT	TR or SM
Ovarian cancer	Epithelial ovarian cancer	Oriana <i>et al.</i> (43)	16	RCT	Reduced GSH	1.5 g/m ²	CDDP	SM
	Stage III (bulky) and IV ovarian carcinoma	Di Re <i>et al.</i> (27)	40	Single arm	GSH	1.5 g/m ²	CDDP, CPA	TR
	Ovarian cancer (Stage III minimal residual disease and localized disease at high risk for recurrence)	Bohm <i>et al.</i> (28)	35	Single arm	GSH	5 g (low-volume hydration)	CDDP, CPA	TR and SM
	Advanced ovarian cancer (stages III and IV)	Pirovano <i>et al.</i> (29)	32	Single arm	GSH	1.5 g/m ²	CDDP, CPA	SM
	Stage III bulky and IV epithelial ovarian cancer	Di Re <i>et al.</i> (26)	79	Single arm	GSH	2.5 g	CDDP, CPA	TR and SM
	Untreated stage III or IV epithelial ovarian cancer	Locatelli <i>et al.</i> (42)	20	Single arm	Reduced GSH	2.5 g	CDDP, CPA	SM
	Relapsed ovarian cancer	Colombo <i>et al.</i> (24)	33	RCT	GSH	2.5 g	CDDP	SM
	Advanced ovarian cancer	Parnis <i>et al.</i> (23)	36	Double-blind, placebo-controlled RCT	GSH	1.5 g/m ²	CDDP	SM
	Epithelial ovarian cancer	Bogliun <i>et al.</i> (40)	54	RCT	Reduced GSH	2.5g	CDDP	SM
	Ovarian cancer (stages I–IV)	Smyth <i>et al.</i> (22)	151	Double-blind, placebo-controlled RCT	GSH	3 g/m ² IV	CDDP	SM
Gastric cancer	Untreated stage III or IV epithelial ovarian cancer	Bohm <i>et al.</i> (44)	50	Single arm	Reduced GSH	2.5 g	CDDP, carboplatin	TR and SM
	Advanced gastric carcinoma (stage III or IV)	Cascinu <i>et al.</i> (32)	50	Double-blind, placebo-controlled RCT	GSH	1.5 g/m ² IV before CDDP + 600 mg IM on days 2–5	CDDP, 5-FU, 4epiDOX, 6S-LCV, G-CSF	TR and SM
	Metastatic gastric adenocarcinoma (elderly)	Cascinu and Catalano (35)	23	Single arm	GSH	1.5 g/m ²	CDDP, 5-FU, 4epiDOX, 6S-LCV, G-CSF	TR
	Unresectable and/or metastatic gastric carcinoma	Cascinu <i>et al.</i> (30)	105	Single arm	GSH	1.5 g/m ²	CDDP, 5-FU, 4epiDOX, 6S-LCV, G-CSF	TR and SM
	Resected gastric cancer at high risk of recurrence	Graziano <i>et al.</i> (34)	25	Single arm	GSH	1.5 g/m ²	CDDP, 5-FU, 4epiDOX, 6S-LCV, G-CSF	TR
	Advanced gastric carcinoma	Cascinu <i>et al.</i> (33)	32	Single arm	GSH	1.5 g/m ²	CDDP, 5-FU, 4epiDOX, 6S-LCV, G-CSF	TR
	Locally advanced, unresectable gastric	Cascinu <i>et al.</i> (31)	82	Single arm	GSH	1.5 g/m ²	CDDP, 5-FU, 4epiDOX, 6S-LCV, G-CSF	TR
	Advanced colorectal adenocarcinoma	Cozzaglio <i>et al.</i> (46)	11	Single arm	Reduced GSH	2.5 g	CDDP, 5-FU	SM
	Advanced colorectal carcinoma	Cascinu <i>et al.</i> (38)	52	Double-blind, placebo-controlled RCT	GSH	1.5 g/m ²	Oxaliplatin, 6S-LCV, 5-FU	SM
	Advanced head and neck carcinoma	Gebbia <i>et al.</i> (45)	22	Single arm	Reduced GSH	1.5 g/m ²	CDDP, 5-FU, folinic acid	TR and SM
Other types of cancer	Advanced HNC and NSCLC	Schmidinger <i>et al.</i> (37)	20	RCT	GSH	5 g (vs. intensive hydration)	CDDP + (etoposide or 5FU)	TR and SM
	Various (advanced)	Nobile <i>et al.</i> (47)	13	Single arm	Reduced GSH	2.5 g	CPA	SM
	Endometrial cancer	De Maria <i>et al.</i> (39)	45	RCT	GSH	1.2 g	RT	SM
	Bulky operable cervical carcinoma (stage IB/II)	Fontanelli <i>et al.</i> (36)	27	Single arm	GSH	2.5 g	CDDP, bleomycin	TR
	Various	Plaxe <i>et al.</i> (25)	16	Single arm	GSH	3.0 g/m ²	CDDP (dose escalating)	TR

GSH								
Cancer type	Cancer type as stated in article	Reference	Pts #	Study type	AO	AO dose	CT or RT	TR or SM
	DTIC-resistant metastatic melanoma	Bajetta <i>et al.</i> (41)	12	Single arm	Reduced GSH	1.5 mg/m ²	CDDP	SM
Vitamin E								
Cancer type	Cancer type as stated in article	Reference	Pts #	Study type	AO	AO dose	CT or RT	TR or SM
Head and neck cancer	Oral cavity and oropharynx cancer (HNC)	Ferreira <i>et al.</i> (51)	54	Double-blind, placebo-control	α-tocopherol	400 mg	RT	SM
	Stage I or II HNC	Bairati <i>et al.</i> (56)	540	Double-blind, placebo-control	dl-α-tocopherol	400 IU daily	RT	TR
Breast cancer	Stage I or II HNC [symptom management aspect of study (40)]	Bairati <i>et al.</i> (57)	540	Double-blind, placebo-control	dl-α-tocopherol	400 IU daily	RT	SM
	Metastatic breast cancer	Lenzhofer <i>et al.</i> (58)	12	Nonrandomized, controlled trial	Tocopherol	200 mg	DOX, nifedipine	SM
Lung cancer	Breast cancer with positive lymph nodes	Martin-Jimenez <i>et al.</i> (55)	25	Nonrandomized, controlled trial	dl-α-tocopherol acetate	1600 IU/day	DOX, FU, CPA	SM
	Stage IIIB NSCLC	Misirlioglu <i>et al.</i> (53)	66	RCT	α-tocopherol	300 mg twice daily	RT, PTX	TR
Other types of cancer	NSCLC or SCLC	Misirlioglu <i>et al.</i> (52)	114	RCT	α-tocopherol	300 mg twice daily	RT, PTX	SM
	Various cancers	Weitzman <i>et al.</i> (54)	16	RCT	dl-α-tocopherol acetate	1800 IU/day	DOX	SM
	Acute myeloid leukemia	Whittaker and Al-Ismail (59)	63	RCT	Vitamin E	200 mg thrice daily	DOX, cytarabin, thiogranine	SM
	Incurable malignancies	Blanke <i>et al.</i> (50)	13	Single arm	d-α-tocopherol	3200 IU/day	5-FU, LCV	TR
	Solid malignancies	Pace <i>et al.</i> (48)	47	RCT	α-tocopherol	300 mg/d	CDDP	SM
	Various cancers	Argyriou <i>et al.</i> (49)	40	RCT	α-tocopherol	600 mg/day	CDDP and/or paclitaxel	SM
NAC								
Cancer type	Cancer type as stated in article	Reference	Pts #	Study type	AO	AO dose	CT or RT	TR or SM
Lung cancer	Lung cancer	Morgan <i>et al.</i> (63)	Unknown	RCT	NAC	1 g every 6 hr	IFX	TR and SM
	NSCLC or SCLC	Loehrer <i>et al.</i> (62)	102	Single arm	NAC	2 g every 6 hr	IFX	TR
Other types of cancer	Inoperable NSCLC	Maasilta <i>et al.</i> (64)	20	Nonrandomized controlled trial	NAC	100 mg/kg IV and 600 mg inhaled before and 30 mg/kg IV after RT	RT	TR
	Various	Myers <i>et al.</i> (61)	54	Nonrandomized, controlled trial	NAC	5.5 g/m ²	DOX	SM
	Stage III colorectal cancer	Lin <i>et al.</i> (60)	14	Placebo-control	NAC	1,200 mg	Oxaliplatin, 6S-LCV, 5-FU	SM

AO, antioxidant; CT, chemotherapy; RT, radiation therapy; RCT, randomized controlled trial; GSH, glutathione; NAC, N-acetylcysteine; CDDP, cisplatin; 5-FU, 5-fluorouracil; LCV, leucovorin; CPA, cyclophosphamide; DOX, doxorubicin; IFX, ifosfamide; PTX, paclitaxel; NSCLC, nonsmall cell lung cancer; SCLC, small-cell lung cancer; HNC, head and neck cancer; TR, tumor-related outcomes; SM: symptom/side effect management or prevention.

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