Antioxidants and Cancer Therapy II: Quick Reference Guide

Davis W. Lamson, MS, ND, Matthew S. Brignall, ND

Abstract

The previous lengthy review concerning the effects of antioxidant compounds used concurrently with radiotherapy and chemotherapy has been reduced to a reference guide. There are only three presently known examples in which any agent classifiable as an antioxidant has been shown to decrease effectiveness of radiation or chemotherapy *in vivo*. The vast majority of both *in vivo* and *in vitro* studies have shown enhanced effectiveness of standard cancer therapies or a neutral effect on drug action. (*Altern Med Rev* 2000;5(2):152-163)

Introduction

This guide is meant to be a companion to the previous review on effects of antioxidant supplementation during cancer therapy.[1] Widespread use of antioxidant compounds makes this an area of increasing interest to oncologists as well as other physicians; hence, the attempt to reduce the findings of a lengthy report to a manageable guide.

Reducing complicated interactions to a single sentence can be an oversimplification. In many instances the effect of an antioxidant compound with a certain therapeutic agent may be specific to a particular tumor type, or may vary with dosage of both antioxidant and chemotherapy. This guide is best used as a means of quickly identifying which antioxidants are likely to be indicated or contraindicated with a particular therapeutic agent. Please refer either to the earlier review (*Altern Med Rev* 1999;4(5);304-329) or the original research reports for more information on these interactions.

Many of these interactions have been studied only *in vitro*. While an *in vitro* result is often a predictor of *in vivo* response, this is not always the case. The interaction between the bioflavonoid tangeretin and tamoxifen is a good example of the risk in placing too much emphasis on *in vitro* evidence. Tangeretin was found *in vitro* to act synergistically with tamoxifen; but *in vivo* tangeretin completely reversed the inhibitory action of the drug on experimental mammary tumors.[2] The authors wish to emphasize that combinations not studied *in vivo* risk potential adverse reactions and should be monitored closely or avoided altogether. Similarly, it must be assumed that any antioxidant found to reduce *in vivo* toxicity of cancer therapy on healthy tissue has the potential to decrease effectiveness of the chemotherapy unless this was specifically studied. The studies reporting reduced toxicity to healthy tissue of a therapeutic agent with unknown effects on treatment outcomes are only reported if the reduction was noted in human studies. The following tables summarize the effect of various antioxidants when combined with specific chemotherapeutic agents or radiation.

Davis W. Lamson, MS, ND
Private practice, Tahoma Clinic- Kent, WA. Coordinator of Oncology, Bastyr University- Kenmore, WA. Correspondence Address: 9803 17th Ave. NE, Seattle, WA. 98115.

Matthew S. Brignall, ND
1999 graduate, Bastyr University. Currently doing a research fellowship at Tahoma Clinic in Kent, WA.
e-mail: mattandmolly@w-link.net

Table 1: Alkylating Agents: cyclophosphamide (CYC), ifosfamide (IFO), busulphan (BUS), melphan (MEL)

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A		Increased therapeutic effect (CYC)[5]		
Beta carotene		Increased therapeutic effect (CYC)[5,18]		
Vitamin C		Increased therapeutic effect (CYC)[19]		
Vitamin E		Increased therapeutic effect (CYC)[20]		
Selenium			Decreased toxicity,* no change in cytotoxic effect (MEL)[21]	*with selenium, zinc, and copper
Coenzyme Q10	Decreased toxicity (CYC+DOC+ 5FU)*[23]	Increased therapeutic effect (CYC+Coriolus versicolor or OK-432)*[22]		*Both studies used combined therapy
Melatonin		Reduced toxicity, no change in therapeutic effect (CYC)[24]		
N-acetylcysteine	Decreased toxicity (IFO)[28,29]	Decreased toxicity, no change in therapeutic effect (CYC)[25,26,27]		
Glutathione (GSH)	Reduced toxicity, possible increased therapeutic effect (CYS+ CIS)[30,31]			
Quercetin		Increased therapeutic effect (BUS)[32]	Increased cytotoxic effect (BUS)[32]	

note: "decreased toxicity" refers to effect on healthy tissue.

Table 2: Antibiotic-type Agents: doxorubicin (adriamycin) (DOX), bleomycin (BLE), epirubicin (EPI), daunorubicin (DAU)

Nutrient	Human Studies	Animal Studies	In vitro studies	Comments
Vitamin A	Decreased toxicity; increased survival (DOX+BLE+ 5FU+MT)[35]		Increased cell differentiation;[33] cells less[33] or more sensitive[34] to DOX	
Beta carotene		Increased therapeutic effect (DOX)[18]		
Vitamin C		Increased therapeutic effect; decreased toxicity (DOX)[19,36]	Increased cytotoxic effect in human breast CA cells (DOX)[37]	Another *in vitro* study using ascorbic acid 2-phosphate found no change in drug-sensitive cells and decreased effect in resistant lines (DOX)[38]
Vitamin E		Decreased toxicity and possible increased therapeutic effect (DOX)[37]	Increased cytotoxic effect (DOX)[40-42]	
Selenium		Decreased toxicity (DOX);[43,44] increased therapeutic effect* (DOX)[45]	No reduction of cytotoxic effect (DOX)[50]	* in drug-resistant tumors
Coenzyme Q10	Decreased toxicity (DOX)[47-49]	Decreased toxicity; no change in therapeutic effect (DOX)[50]		
Melatonin	Decreased toxicity (EPI)[51]			
N-acetylcysteine	No decrease of therapeutic effect; no reduction of toxicity (DOX)[52,53]	Decrease* or no change in therapeutic effect; decreased toxicity (DOX)[54,55]		*First of three *in vivo* studies showing reduced therapeutic effect of chemotherapy with an antioxidant
Glutathione (GSH)	Effective results with GSH plus EPI+CIS+5FU		Increased resistance to drug* (DOX)[56]	*In cell lines with the highest concentrations of glutathione
Green tea		Increased therapeutic effect* (DOX)[58,59]		*In drug-resistant tumors
Quercetin			Increased cytotoxic effect* (DOX, DAU)[60-62]	* drug-resistant cell lines

note: "decreased toxicity" refers to effect on healthy tissue.

Table 3: Antimetabolites: 5-fluorouracil (5-FU), methotrexate (MT)

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A	Decreased toxicity; increased survival (DOX+BLE+ 5FU+MT)[35]	Decreased toxicity; no change in therapeutic effect (MT)[84]		
Beta carotene		Decreased therapeutic effect in fibrosarcoma; no change in squamous cell carcinoma (5FU)[18]*		*Second of three cited *in vivo* studies showing reduced therapeutic effect of chemotherapy with an antioxidant
Vitamin C		Increased therapeutic effect (5FU)[19]		
Vitamin E		Increased therapeutic effect (MT)[40]	Increased cytotoxic effect (MT)[42]	
Selenium		Increased therapeutic effect (MT)[85]		
Coenzyme Q10	Decreased toxicity (CYC+DOX+5FU)[23]			
Melatonin			5FU decreased cytostatic effect of melatonin; effect of combined tx greater than effect of 5FU alone[86]	
Glutathione	Effective results with GSH plus EPI+CIS+5FU[57]	Decreased toxicity; no reduction in therapeutic effect (5FU)[87,88]		

note: "decreased toxicity" refers to effect on healthy tissue.

Table 4: Platinum Compounds: cisplatin (CIS)

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A	Increased therapeutic effect (CIS)[34]		Increased cytotoxic effect (CIS);[34] no change in therapeutic effect (CIS+ETO)[64]	
Vitamin C			Increased cytotoxic effect (CIS)[37]	
Vitamin E		Increased therapeutic effect (CIS)[71]		
Combination Therapy (Beta carotene, A*, C, E)			Increased cytotoxic effect (CIS+TAM+ decarbazine+ interferon)[70]	*13-cis-retinoic acid
Selenium	Decreased toxicty (CIS)[75]	Increase or no change in therapeutic effect, decreased toxicty (CIS)[72,73,74]		
Melatonin	Increased survival, decreased toxicity (CIS+ETO)[67,68*]			*Not significant at high chemotherapy doses
N-acetylcysteine	Possible decrease in toxicity (CIS)[76,77]		Decreased cytotoxic effect (CIS)[78]	
Glutathione	Slight increase or no change in therapeutic effect, decreased toxicity (CIS+CYC);[30,31] (CIS);[79,80,81]			
Genistein			Increased cytotoxic effect (CIS)*[82]	*Against a drug-resistant cell line.
Quercetin		Increased therapeutic effect (CIS)[32,83]	Increased cytotoxic effect (CIS)[32,83]	

note: "decreased toxicity" refers to effect on healthy tissue.

Table 5: Radiotherapy

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A	Increased therapeutic effect, decreased toxicity[4]	Increased therapeutic effect, decreased toxicity[5]	Increased therapeutic effect, decreased toxicity[3]	
Beta carotene	Decreased toxicity, no change in therapeutic effect[6]	Increased therapeutic effect, decreased toxicity[5]		
Vitamin C	Increased therapeutic effect, decreased toxicity[7]	Increased therapeutic effect;[8,9,10] decreased toxicity, no change in therapeutic effect[11]		
Vitamin E		Increased therapeutic effect*[12]		*Doses below 500 mg/kg
Selenium	Decreased toxicity*[13]			*Influence on therapeutic effect unknown
Coenzyme Q10*		No change in therapeutic effect[14]		Doses below 10 mg/kg
Melatonin	increased therapeutic effect, decreased toxicity[15]			
N-acetylcysteine	No change in therapeutic effect or toxicity[16]			
Glutathione	Decreased toxicity, no change in therapeutic effect[17]			

note: "decreased toxicity" refers to effect on healthy tissue.

Conclusion

There are only three presently known examples in which an agent classifiable as an antioxidant has been shown to decrease effectiveness of radiation or chemotherapy *in vivo*. The vast majority of both *in vivo* and *in vitro* studies have shown enhanced effectiveness of standard cancer therapies or a neutral effect on drug action.

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Table 6: Hormonal Therapies: tamoxifen (TAM)

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A	Increased therapeutic effect* (TAM)[90,91]	No change in therapeutic effect (TAM)[89]		*In one study vitamin A enhanced response to TAM in cases where tumor had progressed with TAM alone
Vitamin C			Increased cytotoxic effect (TAM)[70]	
Vitamin E			Increase or no change in cytotoxic effect (TAM)*[92]	*Tocotrienols had greater effect than tocopherol
Mixed: Vitamins C and E, beta carotene, and 13-cis-retinoic acid			Increased cytotoxic effect (CIS+TAM+ decarbazine+ interferon)[70]	
Melatonin	Increased therapeutic effect (TAM)[93]			
Tangeretin		Decreased therapeutic effect (TAM)[2]*		*Third of three *in vivo* studies showing reduced therapeutic effect with an antioxidant

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Table 7: Plant Alkaloids: etoposide (ETO), vincristine (VIN), paclitaxel (TAX)

Nutrient	Human Studies	Animal Studies	In vitro Studies	Comments
Vitamin A	No change in therapeutic effect, (ETO+CIS)[64]		Increased cytotoxic effect (ETO)[63]; Increased cytotoxic effect (VIN)[65]	
Beta-carotene		Increased therapeutic effect (ETO)[18]		
Vitamin C		Increased therapeutic effect (VIN)[19]	Increased cytotoxic effect (TAX);[37] Increased cytotoxic effect (VIN)* [66]	* In drug-resistant cell lines
Vitamin E			Increased cytotoxic effect (VIN)[42]	
Melatonin	Increased survival, decreased toxicity (ETO+CIS)[67, 68*]			*Results not significant at high chemotherapy doses (ETO+carboplatin)

note: "decreased toxicity" refers to effect on healthy tissue.

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