A Strategy for Controlling Potential Interactions Between Natural Health Products and Chemotherapy

A Review in Pediatric Oncology

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Summary: The high prevalence of complementary and alternative medicine use including natural health products (NHPs) in the pediatric oncology population is well established. The potential for concurrent use of NHPs with conventional chemotherapy necessitates physician awareness regarding the potential risks and benefits that might come from this coadministration. Knowledge of interactions between NHPs and chemotherapy is poorly characterized; however, an understanding of potential mechanisms of interaction by researchers and clinicians is important. Concerns regarding the use of antioxidants during chemotherapy are controversial and evidence exists to support both adherents and detractors in this debate. Our review addresses issues regarding potential interactions between NHPs and chemotherapies used in pediatric oncology from a pharmacokinetic and pharmacodynamic perspective. Examples of combinations of NHP and chemotherapies are briefly presented in addition to a strategy to avoid (or induce) a possible interaction between a NHP and chemotherapy. In conclusion, more clinical research is needed to substantiate or preclude the use of NHPs in the treatment of cancer and especially in combination with chemotherapy.

Key Words: natural health products, cancer, pediatric oncology, chemotherapy, complementary and alternative medicine, interaction, pharmacokinetics, pharmacodynamics

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The use of complementary and alternative medicine (CAM) by adult cancer patients is well documented. A systematic review of epidemiologic evidence from 16 different countries found that the use of CAM ranged from 7% to 64% among adult cancer patients with an average use of 31%.[1] The incidence of CAM use by the pediatric population is somewhat less well documented than in the adult population but reports indicate that usage ranges between 31% and 84%.[2] These reports, although not conclusive and based on regional information, indicate that alternative medicine may be sought more often in the pediatric oncology setting than by adult patients with cancer.

There is a tendency for caregivers to make general statements against the use of unproven nonconventional therapies even if these therapies are not harmful. On the other hand, there is an equal tendency for many parents to search for nonconventional therapy that they feel may help their child irrespective of any lack of evidence.[3,4] Parents turn to CAM for children with cancer for a number of reasons. Some of these reasons include: a desire to relieve the burden of side effects caused by chemotherapy; motivation to find a cure; a desire to cover all possible treatment options; and the pursuit of greater personal control over their disease.[2,4,5] Children with relapsed cancer will more frequently turn to the use of CAM than those with an initial diagnosis.[6] Full discussion between patients, parents, and the health care team regarding the use of CAM in cancer is necessary to promote the best health interests of the patient.[7] A failure to engage in such discussions, especially when interest is expressed, will prevent patients and their parents from talking about complementary therapies and may even lead them to abandon conventional therapy entirely.[8]

Conventional therapy is known to cure 70% of pediatric cancer patients. The high rate of cure represents a significant success in comparison to adult cases and it is critical that we understand how CAM therapies may interfere with conventional therapy in the pediatric setting.[9] Natural health products (NHPs) are classified as a broad category of ingested products that are not considered drugs but are thought to be biologically active. NHPs consist of a number of naturally based products that include botanicals, vitamins, minerals, homeopathics, probiotics, essential fatty acids, and amino acids.[10] As exemplified by St John's Wort, a well-known cytochrome P450 (CYP) (ie, CYP3A4) inducer, NHPs demonstrate the potential to interact pharmacologically with many drugs.[11] This review addresses issues regarding combining NHPs with chemotherapy and the potential for both benefit and harm.

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A "drug interaction" is defined as a clinical or pharmacologic response to the administration of a combination of drugs that is different from the effects that are expected when the drugs are administered individually. The term drug interaction usually has a negative connotation arising from an often-reported increase in toxicity or loss of therapeutic activity. Drug interactions, however, may also provide clinical benefit. Certain combinations of agents have been shown to improve outcomes, reduce costs, increase compliance, or reduce side effects.[12]

There is very little information in the medical literature regarding the frequency and type of pharmacologic interactions that may occur when NHPs are used with chemotherapy in patients with cancer. This lack of information is most pronounced in pediatric oncology. At present there are no widely accepted standards to discover and document adverse events that arise either from the use of NHPs alone or from the combination of NHP and chemotherapy. Distinguishing adverse events caused by NHPs versus those caused by chemotherapy also adds to the complexity. This complexity is compounded when a child takes a mixture of drugs wherein multiple permutations of potential interactions and drug adverse effects might occur.

In addition to these issues, there is also a critical lack of clinical research regarding drug/NHP interactions.[13–16] Powerful laboratory techniques provide evidence of potentially important interactions.[17,18] Although it is an essential first step, the preclinical setting provides lower level evidence that cannot be extrapolated to the clinic without being backed up by human studies.[15,17–19] In light of the current lack of evidence, our knowledge regarding pharmacokinetic interaction is unfortunately mostly based on theory.

In this review, we explore mechanisms whereby NHPs may interact with chemotherapy and apply some of this knowledge to devising a strategy to control for potential interactions. The discussion begins with potential benefits and harms attributable to NHPs in cancer followed by a review of some of the more important means of interactions between NHPs and chemotherapeutic agents. Emphasis is placed on the antioxidant debate, and interactions distinguished based on whether the mechanism of interaction is pharmacokinetic or pharmacodynamic. In addition to the potential for harm, arguments for the beneficial integration of NHP use with chemotherapy are also discussed. Specific references to interactions between NHPs and chemotherapy are made in the text and in Table 1. We have chosen a set of representative NHPs based on relative frequency in the literature, clinical experience, and from communications within the oncology clinic and with the pharmacy at the Hospital for Sick Children in Toronto. The total number of NHPs used by cancer patients is vast, and our inclusion of specific examples is not meant to be comprehensive but rather to provide a basis to better understand the relevant issues.

NHPs: RATIONALE FOR USE AND RESEARCH

It is well known that NHPs are taken by cancer patients of all ages, yet it is unclear whether or not these products should have a place in the treatment of cancer. There are widespread anecdotal claims of success from combining NHPs in the treatment of cancer on the Internet and in nonpeer reviewed literature. Such unproven and low-level evidence should not necessarily be discounted, but rather on a case by case analysis seen as a challenge for further investigation. A large body of traditional knowledge exists regarding NHPs' role in the treatment of cancer, especially throughout Asia as reviewed in this journal and elsewhere.[39–41] There is an abundance of preclinical data and some clinical research that demonstrates anticancer activity for many NHPs. A few that have been studied extensively in the laboratory include melatonin,[42] curcumin,[43] whey protein,[44] green tea,[45] fish oils,[46] selenium,[47] vitamin A,[48] vitamin C,[49] and vitamin D.[50]

Epidemiologic evidence of cancer prevention is readily available as exemplified by selenium and green tea,[51,52] but as yet there is little evidence from high-quality randomized controlled trials regarding the effective use of NHPs to treat cancer. One exception to note is melatonin, a supplement that is identical to the hormone produced by the pineal gland. In a recent systematic review and meta-analysis, we demonstrated significant reductions in 1-year mortality when melatonin was combined with conventional treatment in a variety of cancer types. Based on results pooled from 10 randomized controlled trials, the survival protection was dramatic with a combined relative risk reduction of 34% (relative risk = 0.66; 95% confidence interval: 0.59-0.73).[53] Relevant within this context was the finding that melatonin was also responsible for reducing the severity and incidence of adverse effects attributable to chemotherapy.[53]

The possibility that NHPs may also be responsible for causing harm must not be excluded from this discussion. The potential for harm may in fact occur irrespective of any interaction with conventional treatment but instead result through the stimulation of neoplastic tissue theoretically inducing a more aggressive cancer. There are examples in the literature whereby a NHP seems to have this effect. Situations where this has arisen include the promotion of tumors in mice by vitamin E[54]; and increased leukemia cell survival when exposed to herbal extracts, including mistletoe.[55] This phenomenon may have taken place during the Beta-Carotene and Retinol Efficacy Trial (CARET). Findings from the CARET, a large randomized controlled trial, demonstrated a statistically significant increased risk of lung cancer and mortality in the group given a combination of β-carotene and vitamin A.[56] The majority of preclinical research that we found supports an anticancer role for most NHPs, however, the results from the CARET requires a degree of skepticism and strengthens the basis for conducting clinical research before translating results from the bench to the bedside.

TABLE 1. Examples of NHPs' With Evidence of Enhanced Cytotoxicity in Neoplastic Cells and Evidence of Concomitant Protection of Normal Tissue When Combined With Chemotherapy

NHP	Evidence of Antitumor Effect When Combined With Chemotherapy	Effect on Normal Tissue When Combined With Chemotherapy
Melatonin	1. Concurrent administration of melatonin with irinotecan in 30 metastatic colon cancer patients demonstrated a significantly higher percent of disease-control in patients than in those on chemotherapy alone[20]* 2. Concomittant administration of melatonin in 250 adult patients with various cancers treated with different chemotherapies resulted in significantly improved 1-year survival over those who received chemotherapy alone. The combined melatonin and chemotherapy also significantly reduced the frequency of thrombocytopenia, neurotoxicity, cardiotoxicity, stomatitis, and asthenia[22]*	1. Administration of melatonin during or 1 hour after administration of doxorubicin demonstration protection on human peripheral blood stem cells[21] 2. Administration of melatonin before and after anthracycline exposure was found to exert a protective effect on cardiac muscle cells in rats. Effect was particularly evident after acute doxorubicin or subchronic daunorubicin intoxication[23]
Green tea	1. Green tea constituent, theanine, specifically increased tumor adriamycin concentration 2.7-fold in M5076 ovarian sarcoma in mice[24] 2. Theanine increased idarubicin-induced antitumor activity in leukemia model of P388 bearing mice[25]	1. Theanine decreased adriamycin concentrations in non-neoplastic tissue in mice[24] 2. Theanine ameliorates idarubicin-induced toxicity in P388 bearing mice[25]
Curcumin	1. Pretreatment with curcumin-enhanced vinorelbine-induced apoptosis in human squamous cell lung carcinoma H520 cells[26] 2. Consumption of curcumin by mice with human breast cancer xenografts significantly decreased metastases to the lung[28]	1. In vitro study: curcumin improved villous atrophy normally seen in the small intestine upon treatment with methotrexate[27]
Selenium	1. Numerous chemotherapies found to have increased antitumor potential when coadministered with either 5-methylselenocysteine or seleno-L-methionine in mice and rats with tumor xenografts[29] 2. Selenium compounds prevent cisplatin-induced drug resistance in mice with human ovarian tumors[31]	1. Administration of selenokappacarrageenan 4 days before and up to 4 days after cisplatin administration lead to reduced nephrotoxicity and bone marrow suppression compared with control group[30]*
Vitamin C	1. Combination of vitamin C with 5-Fu or cisplatin significantly enhanced cytotoxicity compared with each drug individually in esophageal cancer cell lines OE33 and SKGT-4[32] 2. Administration of high-dose vitamin C in combination with 5-FU enhances cancer cell chemoresponsiveness especially in chemo-resistant cell lines in mouse lymphoma model[34] 3. Vitamin C-enhanced 5-FU and bleomycin cytotoxicity against mouse neuroblastoma cells, however, the same exposure reduced the cytotoxic effect of methotrexate[35]	1. Demonstrated dose-dependent protection against cisplatin-induced nephrotoxicity in a rat model[33]
Whey protein	1. In vitro I Hep G2 cells, Immunocal, a whey protein isolate, enhanced the cytotoxicity of baicalein by inducing more apoptosis[36] 2. Tentative evidence from a small clinical study indicating that whey protein may deplete tumor cell glutathione levels thereby reducing chemoresistance[38]	1. Topical application of an extract containing bovine whey protein protected against 5-FU–induced oral mucositis in hamsters[37]

*Randomized controlled trial.

MECHANISMS OF INTERACTION BETWEEN CHEMOTHERAPY AND NHPs

Physico-chemical Considerations

An important consideration in the area of drug/drug and drug/NHP interactions includes the potential for physico-chemical or "pharmaceutical" interactions. The bioavailability of a therapeutic agent is important for obvious reasons and when coingestion of a NHP with orally dosed chemotherapy occurs, there exists the possibility for alterations in the bioavailability of the chemotherapeutic agent. Potential physico-chemical mechanisms of interaction include the NHP having effects on chemotherapy with respect to absorption, adduction, and adsorption.[12] These issues are of most concern where oral administration of both the chemotherapy and NHP take place within a short time frame. In the case where chemotherapy is administered by injection, this area of potential interaction is fortunately not relevant.

Pharmacokinetic Considerations

The potential for NHPs to interact with chemotherapy has been reported in adults and may reduce the effectiveness or exacerbate the toxicity of prescription drugs.[57,58] The only clinical trial that has measured the interaction between a NHP and chemotherapy was one that examined the impact of St John's Wort on plasma concentrations of SN38, the active metabolite of irinotecan.[57] This small trial demonstrated that St John's Wort reduced the systemic exposure to SN38 by 42% (95% confidence intervals: 14% to 70%). Decreases of this magnitude could result in drug failure and the study concluded that patients should not take the 2 agents together. Mechanisms for interaction include the fact that

TABLE 2. NHPs Anticancer Claims and Pharmacokinetic Profile

NHP	Anticancer Claims	Antioxidant Properties	Half-life	Effect on Drug Transporters	Effect on Cytochrome P450 Metabolizing Enzymes
Melatonin	Immunostimulant, antiangiogenic, anticachectic, antiproliferative[53]	Well established[87]	< 1 h[88]	Possible inhibitory effect on P-glycoprotein mediated doxorubicin efflux[89]	Metabolized by and potential inducer of CYP1A2[90,91]
Green tea	Apoptotic, antiproliferative, antimetastatic, antiestrogenic, antiangiogenic[52]	Well established[92]	3.4 ± 0.3 h for epigallocatechin gallate (most active and longest lived catechin constituent in green tea)[93]	Preclinical evidence of P-glycoprotein inhibition in drug resistant cancer cells[79,94]	No apparent activity on CYP2D6 or CYP3A4[95] Lung microsome model found epigallocatechin gallate to inhibit the activities of CYP1A1, 2B1 and 2E1[96]
Curcumin	Immunostimulant, antiangiogenic, anti-inflammatory, antiproliferative[43,97]	Well established[98]	< 1 h when given with piperine (agent used to increase bioavailability)[99]	Potential inhibitory effect on P-glycoprotein vincristine efflux[100]	Potential inhibitor of, CYP1A1, CYP1A2, and CYP2B1[101]
Selenium	Antioxidant, radioprotective, anticarcinogenic, antiproliferative[102]	Well established[102]	252 d for selenomethione and 102 d for selenite[103]	No evidence of direct effect on P-glycoprotein found	Selenium-enriched garlic had no apparent effect on CYP1A1, 1A2, 2B1, 2E1, and 3A4; however, glutathione S-transferase and uridine 5′-diphosphate-glucuronyltransferase activities were elevated 2-fold to 2.5-fold in rat liver and kidney
Vitamin C	Immunostimulant, anticarcinogenic, antimetastatic[104]	Well established[104]	30 min for high-dose vitamin C[105]	Evidence to support inhibition of P-glycoprotein[106–108]; one study found P-glycoprotein expression to be enhanced by vitamin C[109]	High-dose vitamin C found to have no clinically significant effect on CYP3A4 activity[110]
Whey protein	Immunostimulant, anticarcinogenic, antiproliferative, antiangiogenic[74,111]	Indirectly through the generation of intracellular glutathione[112]	Not applicable. Peptides from whey protein used in anabolic metabolism	No evidence of direct effect on P-glycoprotein found.	Potential inducer of P450 (CYP)1A1 and 1A2 enzymes[113,114]

St John's Wort is a potent inducer of hepatic CYP3A4 and P-glycoprotein.[59–61] Such high potential for interaction of this NHP with the many drugs that are metabolized by CYP3A4 or are substrates of P-glycoprotein should be considered carefully when planning treatment strategies.

Working in the opposite direction, a case report described the accumulation of an experimental irinotecan analog that may have occurred due to NHP ingestion in a recently conducted phase 1 clinical trial.[62] In this trial, an irinotecan analog was found to have a clearance rate that was reduced 5-fold in a single patient. It was suggested that Essiac (a distinct and easily available polyherbal NHP marketed specifically to cancer patients) may have been responsible for the reduced clearance and increased toxicity of the chemotherapeutic agent.[62] As a case report, this evidence is anecdotal and inadequate by itself to make any real inference regarding interaction. However, in the absence of more information, this simple case stands out next to the paucity of clinical evidence regarding NHP/chemotherapy interaction to be found in the literature.

Evidence based on in vitro affinities of NHPs to specific CYP450 enzymes indicates the potential for clinically relevant interactions with chemotherapy.[18] This issue is important to understand as chemotherapeutic drugs are either inherently active or are prodrugs that require in vivo metabolism to activate them. Toxicity is also directly mediated by the CYP450 enzyme system depending on whether these enzymes are involved in the metabolism, detoxification, or elimination of chemotherapeutic agents. Metabolism of drugs (active or prodrug) will invariably produce metabolites that also express different gradients of activity and toxicity. In the area of pediatric cancer, wherein chemotherapy works within a narrow therapeutic window, pharmacokinetic fluctuations can have serious consequences.

Table 3 provides a summary of pharmacokinetic data for some chemotherapy drugs commonly used in pediatrics. Assumptions of whether or not pharmacokinetics of an agent will be altered when concomitant NHP exposure is present depend on knowing if the drug is a prodrug and if it requires activation or not. If activation is required, the question remains; which enzyme(s) are

responsible for activation and is there evidence that a specific NHP will impact the activity of the enzyme? Issues regarding dose and timing of exposure are also crucial. In the case where a NHP and chemotherapeutic agent both have extremely long half-lives, there is clearly a wider window of opportunity for the 2 to interact. On the other hand, if an intravenously administered chemotherapy has a rapid elimination rate as indicated by a short half-life, then the therapeutic effect is realized over a briefer window. A somewhat delayed exposure to a NHP will thus be much less likely to elicit a clinically relevant interaction. This should apply in the same manner if the NHP is ingested before chemotherapy; in this case the half-life of the NHP becomes the limiting variable in terms of risk reduction (Fig. 1).

Modulation of the CYP450 enzymes is the major concern with regards to phase 1 metabolism and the primary activation or deactivation of drugs. Often overlooked, however, is the potential to alter the pharmacokinetic parameters of drug elimination.[63] For instance, the activity of uridine diphosphoglucuronosyltransferases (UGTs) a system of enzymes primarily responsible for phase 2 metabolism can also be altered by the ingestion of NHPs.[18] The UGTs consist of 16 isoforms and are most involved in phase 2-mediated elimination of a number of endogenous and exogenous metabolites. Although more research is needed, alterations in expression or activity of the UGT enzymes are not as likely to result in an interaction as there is much greater substrate overlap in this family of enzymes in comparison to the cytochrome P450 enzymes.[63]

Pharmacodynamic Considerations: The Antioxidant Debate

The issue of concurrent administration of antioxidants to patients receiving chemotherapy is one that has generated a great deal of controversy.[60,64–68] There are valid concerns as to how antioxidants might interfere with the therapeutic efficacy of chemotherapy, however, the potential for some of these agents to offset any toxicity and side effects of chemotherapy is a potent attractor. As with most controversial topics, the argument is supported on both sides. There is a good deal of contradictory preclinical evidence and as yet too little clinical evidence to provide conclusive evidence.

Antioxidant depletion due to treatment with certain chemotherapy such as platinum compounds, anthracyclines, and alkylating agents has clearly been established and is implicated in the development and severity of adverse effects. In a systematic review exploring the effect of antioxidant supplementation with conventional cancer therapy, it was observed that total antioxidant status drops during treatment.[69] In an observational study of children treated with combination chemotherapy for acute lymphoblastic leukemia, it was found that children with higher plasma antioxidants had fewer complications than those with lower antioxidant status.[70] The improvements in the former group included: fewer infections, improved quality of life, reduced toxicity, and fewer days spent in hospital. In addition, the ability to maintain higher doses of chemotherapy was evident in the group with more antioxidants as they experienced fewer dose reductions and less delays in their treatment schedule.[70]

Proponents of concurrent antioxidant use point out that human studies show that antioxidant supplements protect healthy cells from the toxic effects of chemotherapy drugs without also protecting cancer cells. Table 1 summarizes a number of NHPs that demonstrate this kind of beneficial protective effect. On the other hand, those who argue against antioxidant use with chemotherapy are concerned that antioxidants will interfere with the cancer killing effects of the cytotoxic chemotherapy drugs either directly, or theoretically, by inducing a NHP/drug interaction.[61,71] Unfortunately, very few high-quality randomized controlled trials have investigated the effects of concomitant chemotherapy-antioxidant administration on survival. Parents and their children are left with a difficult dilemma. Should they take antioxidants to help protect healthy cells against chemotherapy's proven toxicity, or should they avoid all antioxidant supplementation because of the possibility that they will attenuate the cancer killing effects of chemotherapy?

To further complicate matters, certain NHPs may augment the efficacy of some chemotherapy agents. An example of this includes work that members of our team have conducted on whey protein and other cysteine precursors.[72,73] It seems that modulation of glutathione levels is achieved by the ingestion of these agents. Glutathione, a potent antioxidant, seems to be concentrated in cancer cells and is one of the mechanisms by which cancer cells acquire drug resistance to chemotherapy. Interestingly, ingestion of whey protein causes depletion of glutathione in cancer cells (chemosensitization), while at the same time increasing glutathione production in healthy cells (chemoprotection). Therefore, the action of whey protein or cysteine precursors may be doubly beneficial.[44,72–75] Chemotherapy drugs (particularly the alkylating agents, anthracyclines, platinum compounds, and topoisomerase II inhibitors) often exert their therapeutic (and toxic) effects by forming reactive oxygen species and free radicals. In theory, it is thought that antioxidants may reduce the efficacy of anticancer agents by quenching free radicals but there are several examples of adjunctive agents, such as mesna[76] and amifostine,[77] whose protective effects are attributed to the quenching of free radicals and yet they do not seem to decrease the efficacy of chemotherapy. Supplementation of individuals receiving chemotherapy with antioxidants may be viewed as a parallel to leucovorin rescue of patients being treated with high-dose methotrexate.

Pharmacodynamic Considerations: Modulation of Cancer Cell Chemosensitivity

In addition to the potential impact NHPs may have on chemotherapeutic effect on cancer cells and normal cells, there also exists the potential for the NHPs to modulate cellular resistance to chemotherapy. Synergy between a NHP and chemotherapy could lead to

TABLE 3. Pharmacokinetic Profile and Activation of Chemotherapeutic Agents Used in Pediatric Oncology

Chemotherapy	Cellular Target (Class)	Metabolic Activation?	Key PK in Children	Enzymes Involved
Cyclophosphamide	DNA (alkylating agent)	Yes—cyclophosphamide is a prodrug metabolized by CYP450s to form 4-hydroxycyclophosphamide (source of phosphoramide mustard—the alkylating agent)[115–119]	Large interindividual and intraindividual variation Mean or median $t_{1/2}$ = 3.2-4.1 h ($t_{1/2}$ may increase as dose increases) Mean or median total body clearance = 35.7-48.5 mL/min/m^2 (renal clearance accounts for 25%) Metabolite data have not been reported[121]	CYP2B6, CYP2C family and CYP3A4[120]
Ifosfamide	DNA (alkylating agent)	Yes—ifosfamide is a prodrug metabolized by CYP450s to form 4-hydroxyifosfamide (source of ifosforamide mustard—the alkylating agent)[122,123]	Large interindividual and intraindividual variation Mean elimination $t_{1/2}$ = 2.1 ± 0.9 h Mean total body clearance = 84 ± 27.7 mL/min/m^2 (renal clearance accounts for 13%) (after a 72 h continuous infusion of 3 g/m^2/d) Mean isophosphoramide mustard area under curve = 1.78 (range 0.24–3.78) mM/h Other metabolite data have not been reported[121]	CYP3A4, CYP3A5[120,121]
Carboplatin	DNA (forms interstrand crosslinks)	No—the active form is the free (nonprotein bound) drug and carboplatin is eliminated unchanged by the kidneys[124,125]	Based on ultrafilterable carboplatin in plasma: $\alpha t_{1/2}$ = 0.3-0.9 h $\beta t_{1/2}$ = 1.2-3.6 h[126–128] Mean or median total body clearance = 46-93 mL/min/m^2 [121]	
Cisplatin	DNA (forms interstrand crosslinks)	No—the active form is the free (nonprotein bound) drug. There is some hepatic metabolism but it is not fully characterized[121]	Based on free cisplatin in plasma: Mean total body clearance = 233 ± 455 mL/min/m^2 Free cisplatin elimination $t_{1/2}$ = 0.6-1.5 h Total cisplatin elimination $t_{1/2}$ = 44-418 h[121]	
Methotrexate	DNA (antimetabolites (folic acid analog) that interfere with DNA synthesis)	No—methotrexate is the active compound but hepatic metabolism does result in 7-hydroxy-methotrexate[121]	Mean clearance = 78–91.6 mL/min/m^2 (at higher doses and increasing age, clearance decreases) (renal clearance accounts for 25%)[121]	
Cytarabine	DNA (antimetabolite)	Yes—an anabolic pathway activates cytarabine to the active intracellular form of ara-CTP. A catabolic reaction deaminates cytarabine to its inactive metabolite uracil arabinoside[121]	IV infusion of 3 g/m^2 over 1 h resulted in: Mean elimination $t_{1/2}$ = 4.04 ± 3.1 h Mean area under curve = 386.8 ± 328 μMh C_{max} range = 57-199 μM[121]	Deoxycytidine kinase, and cytidine deaminase[121]
Doxorubicin	DNA (anthracycline)	A less active metabolite is doxorubicinol	Large interindividual variation Mean elimination $t_{1/2}$ = 17.6-21.2 h Mean systemic clearance = 1443 mL/min/m^2 [121]	CYP2D6
Etoposide	DNA and proteins	Yes—etoposide is metabolized by CYP3A4 to form a catechol metabolite which ultimately generates the damaging hydroxyl radicals[129]	Large interindividual variation $\alpha t_{1/2}$ = 41-49 min $\beta t_{1/2}$ = 2-6 h[75,129–132] Mean systemic clearance = 19.5-25.9 mL/min/m^2	CYP3A4

			Mean volume of distribution = 4.8–7.2 L/m^2 (renal clearance accounts for 45%).[121] Oral administration results in similar blood concentrations as short-term IV therapy[133]	
Vinblastine	Microtubules (tubulin inhibitor that functions to inhibits cell cycle progression and induces apoptosis)[121]	No—vinblastine is the active compound but desacetylvinblastine has been identified as at least one of the metabolites[121]	Not studied[121]	CYP3A4[121]
			In adults: large interindividual variation Mean terminal elimination $t_{1/2}$ = 25 ± 16 h to 29 ± 11 h Mean total body clearance = 552 ± 162 mL/min/m^2 (clearance may be dose-dependent)[121]	
Vincristine	Microtubules (tubulin inhibitor that functions to inhibit cell cycle progression and induces apoptosis)[121]	No—vincristine is the active compound but it is eliminated primarily by hepatic metabolism[121]	Large intraindividual and interindividual individual variation	CYP3A4[121]
			Mean elimination $t_{1/2}$ = 13.7 ± 6.5 h to 18.7 ± 18.8 h Mean total body clearance = 357 ± 146 to 482 ± 342 mL/min/m^2 [121]	
Topotecan	Topoisomerase I	No—it is eliminated primarily via the renal route without minimal metabolism[134] but some *N*-desmethyl topotecan is formed by a minor hepatic metabolic pathway. Both topotecan and *N*-desmethyl topotecan have a α-hydroxy lactone moiety in the E-ring that undergoes pH-dependent reversible hydrolysis to form the carboxylate form.[135] The lactone is the active form[134]	$\alpha t_{1/2}$ = ~30 min[136] $\beta t_{1/2}$ = 3-7 h[124,134,136,137] Cl = 16.2-19.6 L/h/m^2 [124,136,137]	
Irinotecan	Topoisomerase I	Yes—it is deesterified by carboxylesterases[138] to form SN-38 which is a much more potent topoisomerase I inhibitor. Irinotecan and SN-38 undergo pH-dependent reversible hydrolysis to form an active lactone species to a relatively inactive carboxylate[139–141]	Mean $t_{1/2}$ = 2.7-11.7 h[139,141]	CYP3A4 converts irinotecan to minor metabolites 7-ethyl-10-[4-N-(5-aminopeptanoic acid)-1-piperidino]-carbonyloxycamptothecin, and 7-ethyl-10-(4-amino-1-piperidino) carbonyloxy-camptothecin[139,140]
			Mean or median Cl/F = 13.6-74.1 L/h/m^2 [139,140,142,143] Mean SN-38 $t_{1/2}$ = 1.6-9.9 h[141–143]	
Temozolomide	DNA (methylating agent)	Yes—spontaneous hydrolysis at physiologic pH to from the active methylating species 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC)[138,144,145]	$t_{1/2}$ = 1.5-2.7 h Cl/F = 3.3-8.2 L/h/m^2 [144,145]	

enhanced cancer cell cytotoxicity by reducing cellular chemoresistance. There are numerous experiments in the literature that demonstrate this potential when cancer cell lines are subjected to both NHP extracts and chemotherapy agents, some of which are described in Table 1. The cellular agent most often implicated in this process is P-glycoprotein, a transmembrane drug efflux protein. P-glycoprotein was discovered early on to be a common and important component of the multidrug-resistant (MDR) cell phenotype.[78] To elucidate how a NHP might modulate P-glycoprotein, an example of this phenomenon in vitro is described.

In a study by Mei et al,[79] polyphenol catechins of green tea enhanced the cytotoxic effect of doxorubicin in a carcinoma cell line over 5-fold in a *drug-resistant* cell line. Of particular interest is the fact that this synergistic effect was not demonstrated in a *drug-sensitive* carcinoma cell line. Further investigation by this group demonstrated that MDR1 gene expression was reduced in the *drug-resistant* cell line thereby inhibiting the expression of its protein product, P-glycoprotein.[79] The net result of hindering P-glycoprotein is what ostensibly led to a decrease in elimination of the doxorubicin with a resultant increase in intracellular doxorubicin concentration and increased cytotoxicity. In juxtaposition, the *drug-sensitive* cell line did not express the P-glycoprotein and hence did not experience any change in sensitivity when coexposed to green tea polyphenols and doxorubicin. It is encouraging that the concentration of green tea catechins used in this study are in fact achievable in vivo.[80]

STRATEGY TO CONTROL POTENTIAL INTERACTIONS

In principle, it takes 5 half-lives to reach steady state and 5 half-lives to eliminate virtually all of a drug from the body. Knowing the half-lives of both NHP and chemotherapy can allow for a dosing regimen to be designed that will theoretically ensure that both agents are not present in the blood stream at the same time. Figure 1 depicts 3 possible scenarios of NHP-drug combinations. In Figure 1A, the likelihood of interaction is strongly reduced, as administration of the NHP is stopped and sufficient time is allowed for the NHP to washout before exposure to IV chemotherapy. The same applies posttreatment with an adequate wash out period of the chemotherapy drug before NHP ingestion resumes. In Figure 1B, a different situation is depicted. In this case the NHP is given right up to and immediately after chemotherapy thereby greatly increasing the risk of interaction. Finally, in Figure 1C, the greatest risk for interaction is depicted should NHP ingestion not be stopped at all during chemotherapy administration.

In the case where we cannot predict if an interaction is likely to occur or not, many clinicians would argue that the prudent choice is to ensure that the first situation (Fig. 1A) is maintained. Chemotherapy is highly toxic with a narrow therapeutic window and it is critical that its efficacy and toxicity profile not be inappropriately modified. In the case where an assumed benefit occurs through concurrent use of NHP and chemotherapy, then the third situation (Fig. 1C) may in fact be desired with no delay between NHP and chemotherapy advised. Some NHPs seem promising in their ability to reduce toxicity to normal tissue and even may synergize with a chemotherapeutic agent. However, there are as yet no combinations of NHPs and chemotherapy that we can say with certainty will lead to clinical benefit and not result in harm.

The window for pharmacokinetic interaction is also modified by the length of time the metabolizing enzymes may be induced or inhibited. Inhibition of drug metabolizing enzymes can be classified as reversible, quasi-irreversible, or irreversible. Most often, drug interactions result due to competitive reversible inhibition.[12] When this situation arises we can expect that inhibition will last only as long as the inhibitor is present. Thus, the half-life is a reliable estimator of the potential window of interaction and inhibition should not last longer than the time required for substrate (NHP) clearance. In the case where metabolizing enzymes are down-regulated by irreversible inhibition, the window of interaction may expand beyond the range of 5 half-lives. Thus, a more conservative approach is required to establish a safe time frame for NHP avoidance before commencing chemotherapy.

In the case of induction, changes in enzyme expression result from increased DNA transcription and synthesis of CYP450 enzymes. The time course of induction also depends on the elimination half-life of the inducer and the time required for enzyme degradation and new enzyme production.[12] As opposed to competitive enzyme inhibition, CYP450 induction will likely have a carry over or ''hangover'' effect. A longer delay before chemotherapy may thus be a wiser course if enzyme induction is expected. Figure 2 depicts drug concentration changes in the presence of inducers or inhibitors. In the case of chemotherapy drugs with narrow therapeutic windows, the potential for toxicity or therapeutic failure is especially high.

Nonchemotherapeutic drug-based interactions can also be very important and concerns have been raised with regard to combining certain NHPs with immunosuppressant drugs and anticoagulants in particular. These issues are further reviewed in a number of excellent resources.[2,81,82] The specific concern toward the use of immunostimulant NHPs in conjunction with stem cell transplantation is also important due to the possibility of increasing the likelihood of rejection.[2,81] A large number of NHPs have immunostimulatory activity and some of the more popular ones include: echinacea, ginseng, astragalus, melatonin, whey protein, shitake and maitake mushrooms, and curcumin.[83] No reliable evidence is available to indicate whether these can in fact induce stem cell transplant rejection or not but the consequences of rejection suggest that greater caution be exercised in these cases.

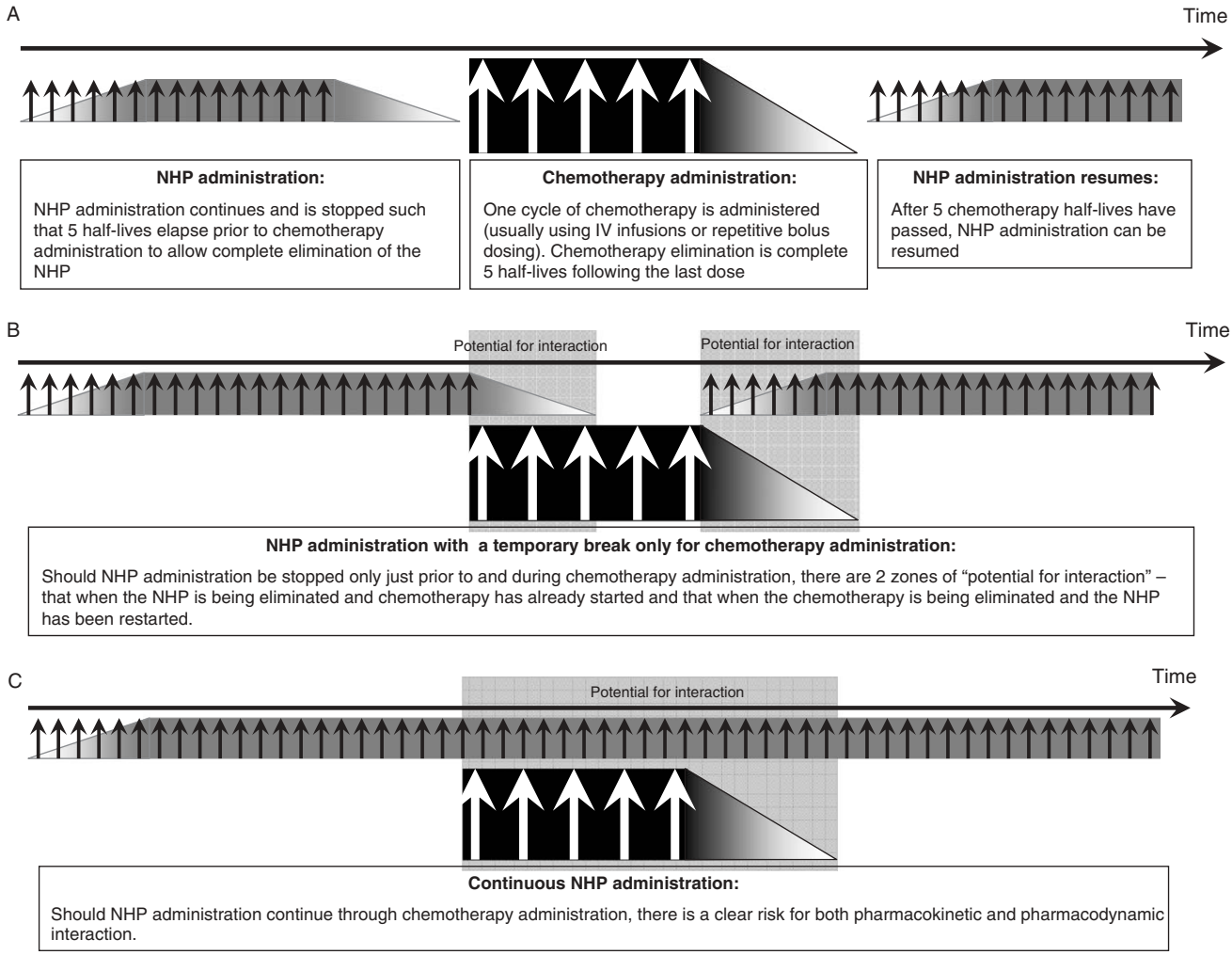

FIGURE 1. Different scenarios depicting staggered or concurrent administration of NHP and chemotherapy and resulting likelihood for pharmacodynamic and pharmacokinetic interaction. Vertical arrows depict points of NHP or chemotherapeutic dosing. A, Least potential for interaction; B, medium potential for interaction; and C, highest potential for interaction.

A related issue in pediatric cancer is the question of whether immunostimulant NHPs might result in the stimulation of leukemia or lymphoma cells. Once again there is a scarcity of evidence in this area, however, at least one NHP with known immunostimulant properties seems not to have this effect. In preclinical studies, melatonin did not induce cancer proliferation in either leukemia[84] or lymphoma[85] models. In addition, results from a clinical trial indicate that melatonin in combination with interleukin-2 prolongs survival in advanced hematologic malignancies.[86]

When to Stop NHP Consumption Before Chemotherapy

The evidence regarding NHPs' effect on metabolizing enzymes is lacking not only with regard to the direction, that is inhibition or induction, but the mechanism of interaction is even more poorly characterized. Consequently, pharmacokinetic interactions between NHPs and chemotherapy are virtually impossible to reliably predict. Uncompromising rejection of NHPs during cancer treatment may elicit a negative response from patients and their families and result in NHP use being undisclosed to their oncologist. A rational approach that respects the wishes of the family and incorporates a strategy to avoid interaction is perhaps the safest course of action. Table 2 demonstrates that the half-lives of the NHPs listed, except for selenium, are less than 4 hours. Thus, 1 day free of *these* NHPs should be adequate for full elimination, and therefore avoid an interaction as depicted in Figure 1A. In addition, there is no evidence that these NHPs affect the CYP3A4 or CYP2D6 isozymes and thus are less likely to alter the metabolism of most of the chemotherapy drugs listed in Table 3. The potential inhibition of P-glycoprotein caused by these NHPs may, however, remain beyond the timeframe required for clearance. Although entirely theoretical, this could in fact have a beneficial

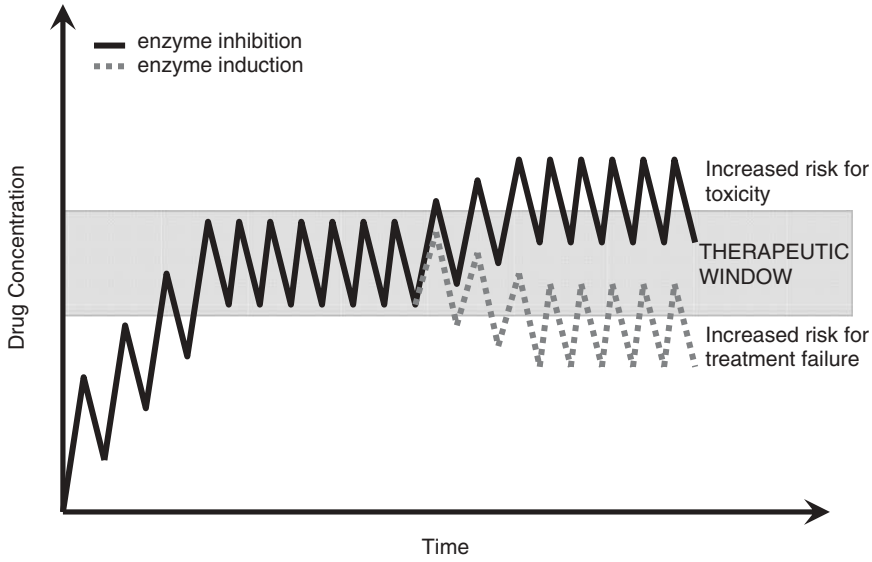

FIGURE 2. Potential deviations of drug concentration out of therapeutic window as a result of enzyme induction of inhibition.

consequence in reducing chemoresistance in cancer cells with the MDR phenotype.

When no information is available as to the half-life of the NHP or on the inductive or inhibitory effect on drug metabolism, greater caution is warranted. Stopping the NHP 1 to 2 weeks before chemotherapy is probably adequate but again must be moderated by patient/family wishes and the comfort level of the physician. In the situation where clear evidence of interaction is available, a situation applicable to St Johns Wort, a strict recommendation to avoid consumption of this product before therapy is indicated. Unfortunately, with respect to clear evidence of interaction, St Johns Wort is *the* exception.

When to Restart NHP Consumption Postchemotherapy

Advice as to when a patient may restart a NHP after chemotherapy should focus in particular on the pharmacokinetic profile of the chemotherapeutic drug. As detailed in Table 3, the half-lives for chemotherapeutic agents used in pediatrics range anywhere from 1 to 30 hours. Typical dosing follows a schedule wherein high doses of chemotherapy are given sequentially followed by a 2 to 3 week rest period. As the therapeutic window is mostly maintained during this sequential dosing, if NHP interaction is uncertain, consumption during this period should be avoided. Once the chemotherapy is stopped, however, and 3 half-lives have elapsed, the therapeutic window will be closed. Based on this rational approach, it is at this time that NHP use can be safely reintroduced.

DISCUSSION

In a survey conducted in the United States, it was found that 84% of children with cancer used some form of CAM therapy.[71] Of perhaps most clinical significance in this study, however, was the fact that more than half of the respondents who used CAM chose to do so during active conventional treatment rather than after having completed treatment.[71] A recent review of research involving CAM therapies in pediatric cancer states that the parents wished that they had more information regarding the use of CAM and NHPs for their children.[146] Concern toward the potential for interaction between NHPs and conventional therapy was considered an important component of the information desired.

Although some CAM therapies such as nutrition, herbs, acupuncture, or manipulation may offer some benefit,[147] it is important for patients to realize that not all interventions labeled as "natural" are necessarily safe especially when they are combined with pharmaceutical agents. For optimal care, physicians should discuss NHP use with their patients. To do so, the physician must have the relevant information to properly advise their patients. It is documented that some NHP therapies are associated with adverse effects.[148] However, information regarding the clinical relevance and risks associated with NHP use is limited and the potential for interaction with chemotherapy is still essentially theoretical. Consumers' reluctance to report adverse reactions, the lack of a detailed reporting system, and the fact that some reported adverse effects are caused by adulterated products may contribute to the information gap.[149]

Strongly related to the topic of NHP/chemotherapy interaction is the need for open nonjudgmental discussion with parents and patients regarding their use of nonconventional medications. Qualitative research highlights patients' desires for physicians to be knowledgeable in the area of CAM and to be willing and able to discuss their knowledge with them.[150] Clearly, the more conversant a physician is regarding CAM and its potential risks and benefits, the more informed, extensive, and open communication can be with both patients and their families. With regard to potential interaction between chemotherapy and NHPs, if the physician has a solid understanding of the issues, they will be much better able to communicate the risks in a truly effective manner. A large proportion of oncology patients do not discuss CAM with their oncologist owing partly to a fear of disapproval

and even refusal to continue treatment in some cases. Another rationale why patients do not communicate their NHP use may be based on an assumption of safety due to the natural aspect of the NHP and a lack of awareness of potential interactions.[151] The oncologist's knowledge and willingness to discuss NHP use is required to minimize these barriers to communication. Through informed and open discussion, the likelihood of complying with physician recommendations is greatly enhanced. By establishing intelligent guidelines as to when and how NHPs can be incorporated with or between chemotherapy sessions (if appropriate), the risk of an interaction leading to increased toxicity or decreased efficacy should be significantly attenuated.

Compounding the issue of NHP/chemotherapy interaction is the inherent heterogeneity that exists across the spectrum of NHPs available. Primarily, NHPs can be differentiated from pharmaceuticals in terms of their molecular makeup. Whereas a typical "drug" is composed of a specific amount of a perfectly characterized molecule along with an inert vehicle of excipients, many NHPs consist of plant material that have been subjected to very little processing.[17] For instance, the molecular complexity of a standardized extract of St Johns Wort is essentially that of a complex organism. Not only are there large number of products with anticancer claims, but for each product on the market, there is great variability in terms of production quality and batch-to-batch consistency.[152] As yet, characterization of NHPs is neither standardized nor required in the industry.[17] NHPs can contain an enormously wide range of molecular compounds, many of which have been determined to be biologically active.[17] In addition, many available products consist of a mixture of herbs, nutraceuticals, vitamins, and minerals. Unfortunately, it is all too common for research conducted on NHPs not to include adequate information regarding the product's chemical composition. As a result, generalizing results from research becomes even more difficult.

Research based on strong pharmacokinetic methodologies is needed to uncover real interactions between chemotherapy and NHPs, especially in the pediatric setting. Venkataramanan and colleagues[18] recently published an excellent and thorough review on the in vitro and in vivo assessment of herb-drug interactions. The limitations and advantages of in vitro, in vivo animal and in vivo human systems are summarized therein. Although the system in which the final answer to the herb-drug interaction question is provided is clearly the human system, significant barriers exist to conducting such research in patients with cancer and this is especially the case for children with cancer.

First and foremost is the difficulty in defining the population of pediatric patients to be studied. The incidence of childhood cancer is relatively low when compared with adults. For example, in Canada, approximately 1300 children are diagnosed with cancer each year. Two hundred forty-one children relapse and of these only 85 are eligible for phase 1 studies. These figures include all patients between the ages of 0 and 19 and all diagnoses of cancer.[153] To design a study that would generate meaningful data, one would ideally strive to select a fairly homogenous group of children. Factors to consider both from a scientific and ethical standpoint include disease subtype and the inclusion of newly diagnosed versus relapsed patients. In the case of relapsed patients, heavy pretreatment with the chemotherapy regimen to be studied may be a confounding factor. A further complication is that once an appropriate population is defined, only a few eligible patients may be available for inclusion, thereby substantially reducing the power of the study. These kinds of trials are still possible with the concerted efforts of organizations such as the Children's Oncology Group—a North American-wide network of pediatric cancer centers.

Another challenge is the selection of which NHP to study and controlling for factors that may contribute to increased variability. These factors include variations in formulation between manufacturers and even variation between lots by the same manufacturer. It is important that for research conducted in this area and for NHPs in general, the composition of the NHP is well characterized or at least standardized to a set of compounds that are considered to be biologically active. In this way results will have greater generalizability and be more reliable when trying to make comparisons with other products containing some of the same constituents.

Furthermore, cocktails of NHPs may be used rather than single products but even in this case, a single product may contain a number of pharmacologically active components that could confound results. Compliance, especially among children, may be less than ideal. NHP use can require the consumption of large amount of tablets/capsules or powders daily, or, even at multiple daily time points that may be difficult to adhere to, especially for younger children.

Should a patient population be defined and a NHP selected, there are still a number of concerns that need to be considered. Interpatient variation with respect to the pharmacokinetics of chemotherapy drugs is high for almost all agents as shown in Table 3. This may be due to the ontogeny or genetic polymorphisms of the drug metabolizing enzymes or other variation which may be attributable to previous therapies, environmental factors, diet, or impaired organ function.[12] In addition to interpatient variation there is also the less well-characterized issue of intrapatient variation in chemotherapy pharmacokinetics from cycle to cycle. The inherent developmental heterogeneity (ontogeny) within the pediatric population also increases pharmacokinetic variability. As such, it may be difficult to establish a causal relationship between chemotherapy pharmacokinetics and NHP coadministration even with a reasonable sample size.

In the absence of solid evidence supporting or disputing the interaction of chemotherapy agents and NHPs, one must rely on pharmacologic principles to estimate, at least in theory, whether an interaction may or

may not occur. As summarized in Table 3, it is clear that CYP3A4 is the isozyme that is most frequently involved in drug metabolism of chemotherapeutics. Contrasting this to the small subset of NHPs summarized in Table 2, it is evident that CYP3A4 is not commonly affected by *these* NHPs. Although the information in Table 2 cannot be extrapolated to all NHPs, it is encouraging to see that the potential for altering the activity of one of the most important drug metabolizing isozymes is probably low. With respect to P-glycoprotein, this drug efflux pump is well known for its implication in drug resistance of cancer cells. Table 2, provides a summary of evidence to suggest that several of the selected NHPs inhibit P-glycoprotein. This might theoretically lead to a potentially beneficial interaction by reducing cancer cell chemoresistance. However, most data regarding alterations in CYP450 enzyme and P-glycoprotein activity is derived from preclinical studies. Laboratory-based experiments often use concentrations in excess of what is clinically achievable and as such the potential to realize a clinically relevant effect is easily overstated.

Finally, from the antioxidant perspective, the ability to predict an interaction based on theory and preclinical evidence is more difficult. Not all chemotherapeutics are oxidants and, therefore, exposure to an antioxidant may have little to no effect on their efficacy. On the other hand, for those chemotherapeutics whose mechanism of action is based on pro-oxidant effects, the possibility exists for a dual benefit from chemo-sensitization and chemoprotection, depending on the cell population. We emphasize the need for methodologically sound and ethically based preclinical and clinical investigations to confirm or disprove some of the theoretical predictions. Phase 1 trials provide an ideal setting to test NHPs for both interaction and efficacy in pediatric oncology before carrying them forward to phases 2 and 3 trials. In a multicentered collaborative group like the Children's Oncology Group, the infrastructure and expertise exists to conduct rigorous phase 1 studies in this area, including the collection of blood samples for appropriate pharmacokinetic analysis.

The area with perhaps the most therapeutic potential for NHPs in pediatric cancer and cancer in general, involves the attenuation of side effects due to chemotherapy and thus improvements in quality of life within this population.[68,154,155] There is evidence to demonstrate that certain agents have the ability to maintain a dual response through an oncolytic or oncostatic effect at the same time as providing protection for normal non-neoplastic tissue.[68,154] As discussed, Table 1 characterizes a subset of NHPs used by children with cancer that have preclinical data and infrequently clinical data regarding specific interactions between NHPs and chemotherapies in both normal and neoplastic tissues. In some cases it has also been demonstrated that the combination of NHPs and chemotherapy results in an inhibition and even reversal of drug resistance. The research is promising but somewhat conflicting as evidenced by the potential for stimulating cancer cell growth. Given the scope of the field, we had to be somewhat selective and this was done with the aim of providing as balanced and unbiased a perspective as possible.

The largest limitation we identified is the recurrent issue that more clinical research is needed. Evidence from human trials is necessary not only with respect to potential interactions, but also to follow up on some potentially beneficial therapies and in some cases possibly harmful agents. In this endeavor, it is important that an effective way of monitoring adverse reactions is in place so that harms and benefits can be identified.

Whereas investigational new drugs need approval before incorporation into clinical practice, NHPs are freely available to the public and consumed in abundance. For good or bad, pediatric cancer patients *are taking* these products and it is imperative that we know the effects they have and also how they interact with conventional treatment. When equipoise is present and actual use is evident, research needs to be conducted to determine the safety and efficacy of specific NHPs in pediatric cancer. To use an analogy from macroeconomic theory, in the case of drug development, it could be stated that both demand and supply are pushing clinical research. Demand by the public for better treatments for cancer, and supply from the pharmaceutical industry to provide public benefit and to maximize market share and profitability. In terms of research for NHPs, the principal drive is demand from the public. A lack of funding from industry support creates the need for publicly funded research in the area of developing nonpatentable medicines and toward establishing safety. The area of NHP/chemotherapy interaction is of great importance due to: a lack of reliable clinical information; a high degree of concordant use of NHPs and chemotherapy; and the narrow therapeutic indices of chemotherapeutic agents. Given what is at stake these concerns are profoundly magnified in the pediatric oncology population.

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