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Potential issues with complementary medicines commonly used in the cancer population: A retrospective review of a tertiary cancer center's experience

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Running Title: Potential issues with CAM in the cancer setting

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Aim: Complementary medicine (CAM) use in the cancer population is higher than the general population: some studies estimate up to 70%. Our Medicines Information Centre, in a tertiary cancer institution, receives many enquiries regarding use and safety of CAM with conventional cancer therapies (chemotherapy, radiotherapy and surgery). This project aims to review the CAM most commonly enquired about with an emphasis on potential interactions with conventional cancer therapies.

Methods: An audit and review of CAM enquiries from patients or medical professionals at our centre, over a 2 year period (July 2011-June 2013) was conducted. The most commonly enquired about CAM, excluding vitamins and minerals were identified, reviewed and potential interactions described.

Results: Enquiries were received from 462 patients involving 330 different CAM. The 10 CAM most commonly enquired about were fish oil (3.54%), turmeric (3.24%), coenzyme Q10 (2.63%), milk thistle (2.44%), green tea (2.38%), ginger (2.14%), lactobacillus (2.08%), licorice (1.83%), astragalus (1.77%) and reishi mushroom (1.59%). All were found to have predicted or potential drug interactions or therapeutic issues when combined with conventional therapies. Human studies are lacking and potential drug interactions are often predicted using in vitro or in vivo animal data.

Conclusions: Whilst many CAM may be safe when taken by themselves, there is theoretically a potential for interactions and/or increased risk of serious adverse effects when taken concurrently with conventional anticancer therapies. The paucity of human data implies their clinical significance is difficult to quantify and hence caution is required.

Keywords

Antineoplastic agents, complementary therapies, herb-drug interactions, neoplasms, radiotherapy

Introduction

The use of complementary medicines (CAM) in the cancer population is increasing, and is higher than in the general population.[1] A 2014 single centre study at an Australian tertiary cancer institution reported the prevalence of CAM use in patients receiving chemotherapy to be 39%.[2] A similar 2011 single centre study conducted in the UK reported the prevalence of CAM use in cancer patients to be 20-25%.[3] A 2012 systematic review and meta-analysis of studies over the past 30 years from 18 countries (>65,000 cancer patients) found the prevalence of CAM use in the cancer population to be 40%.[4] The use of CAM has as expected increased with time, with an estimate of 25% in the 1970s and 1980s to more than 49% after 2000.[4]

Many factors need to be considered when assessing the safety of ingesting a CAM in combination with standard oncological therapies such as chemotherapy and/or radiotherapy, or pre-surgery. Potential sources of adverse effects include those directly from the CAM; either fromthe agents themselves, excipients or contaminants, potential drug-drug or drug-radiation interactions, antioxidant activity, antiplatelet effects, immunomodulatory effects, estrogenic effects. These interactions can either lead to reduced therapeutic drug clearance resulting in increased toxicity or an increase in their metabolism with reduced efficacy or activation of toxic prodrugs. Similarly, they may result in greater toxicity or reduced efficacy of external beam radiotherapy or add to surgical morbidity. Hence, the effectiveness of standard cancer therapy and hence patient outcomes can be severely impacted upon in addition to the potential adverse effect of CAM alone.

CAM related enquiries form a significant portion of a Medicines Information Centre's workload. A referral Drug Information service in the United States quoted 9.7% of enquiries being CAM related.[5] The Medicines Information Centre at Peter MacCallum Cancer Centre, a tertiary oncological referral centre, receives approximately 140 enquiries per month from a range of enquirers including pharmacists, doctors, nurses and patients. A three year review (July 2012 to May 2015) of service statistics found an average of 17% (913 of 5376) of all enquiries were related to CAM and their safety in the cancer setting. Advice is ultimately given on whether it is likely safe for a patient to take a particular CAM or whether it should be avoided and if so, the reason for this and timeframe for withholding or ceasing.

The aim of this project is to review the most commonly enquired about CAM and hence outline and discuss potential therapeutic interactions and/or issues associated with each when used in combination with conventional cancer therapies.

Methods

A retrospective audit and review of the CAM enquiries received by the Medicines Information Centre at Peter MacCallum Cancer Centre over a 2 year period was conducted. Records for all enquiries completed between July 2011 and June 2013 were reviewed and the following information was recorded for those relating to CAM: date of enquiry, CAM products and ingredients (product ingredients were obtained from product label or product webpage), the number of CAM products and compounds generating the enquiry and patient demographics including sex, age, cancer type, new or existing diagnosis, treatment modality and the treatment intent were obtained from the electronic medical record where the patient record number was recorded.

The ten most commonly enquired about CAM, excluding vitamins and minerals were identified and summarised. Vitamins and minerals were excluded from the study as they are often prescribed as conventional therapy and it is not always possible to separate conventional prescribing from complementary use. The potential interactions or problems associated with the use of each CAM in combination with oncological treatment (chemotherapy and/or radiotherapy, or pre-surgery) was researched via a Medline database literature search, keywords: complementary medicine, alternative medicine, cancer, chemotherapy, radiotherapy, surgery and individual CAM name(s) and a search of two evidence based CAM databases, Natural Medicines[6] and the Memorial Sloan Kettering 'About Herbs, Botanicals & Other Products' database[7].

Results

A total of 2665 enquiries were completed over the 2 year period and of these, 462 were CAM enquiries involving a total of 330 different CAM, excluding vitamins and minerals. As shown in Table 1, 42% of enquiries involved 1 CAM product, 41% involved 2 to 5 CAM products and 4% involved greater than 10 products. Many of the CAM products contained combinations of multiple individual compounds with 31% of enquiries involving a single compound, 31% involving 2 to 5 compounds, 16% involving 6 to 10 compounds and 21% involving greater than 10 compounds.

Patient demographics are shown in Table 2. Of the patients with data recorded, the majority of patients were aged over 41 and were female (62%). Overall 57% of patients with data recorded had an existing cancer, 43%

were newly diagnosed, 73% were being treated with adjuvant intent and 27% treated with palliative intent. The majority of enquiries received related to the use of CAM in combination with an anti-cancer agent (56%) followed by an anti-cancer agent combined with radiotherapy (18%).

Figure 1 presents the distribution of CAM enquiries received per cancer type and shows that the most enquires are received from patients with hormone sensitive breast cancer (15%), followed closely by haematological cancers (14%) and gastrointestinal cancer (11%).

The 10 most commonly enquired about CAM,excluding vitamins and minerals were fish oil (3.54%), turmeric (3.24%), coenzyme Q10 (2.63%), milk thistle (2.44%), green tea (2.38%), ginger (2.14%), lactobacillus (2.08%), licorice (1.83%), astragalus (1.77%) and reishi mushroom (1.59%). These low figures reflect the exceptionally high number of different CAM used in the cancer population. The summary of the literature search results for the potential interactions of these 10 most commonly enquired CAM, with standard cancer therapies is presented in Table 3. The interactions and therapeutic issues included in the review reflect those that aremost likely to have clinical significance by potentially affecting conventional cancer therapy. The recommendations relating to how these potential interactions/problems should be managed are detailed below.

Discussion

The decision on whether it is likely safe for a patient to take a particular CAM needs to be made on an individual patient basis by considering the full clinical history of the patient, the concomitant medications the patient is taking, medical comorbidities, end organ function, and the potential effects the CAM may have on their oncological disease, and its multidisciplinary treatment. The aim of this project is to review the most commonly enquired about CAM and hence outline and discuss potential therapeutic interactions and/or issues associated with each when used in combination with conventional cancer therapies. Vitamins and minerals were excluded from the study as they are often prescribed as conventional therapy and it is not always possible to separate conventional prescribing from complementary use.

As summarised above, the lack of high quality data is of the greatest concern. There is a very severe paucity of high level of evidence, published in reputable sources rather than obscure journals, websites, testimonials, etc., regarding the human pharmacokinetics/pharmacodynamics of these agents, the potential and severity of the cancer therapy-CAM interactions, and the direct/indirect effects on cancer biology. Similarly the doses required

to generate an interaction and how translatable they are from the preclinical setting to the human are also difficult to interpret. In addition to such deficiencies, there are also significant issues with the quality of the CAM preparation - the exact content of the active ingredient(s) in the various commercial preparations evaluated, the variability of the formulation itself and its impact on the bioavailability and hence systemic exposure. The commercial preparations can be manufactured from several sources across different continents with surprisingly very little or no legislative regulation controlling their manufacture at any point. In Australia, the majority of complementary medicines are listed on the Australian Register of Therapeutic Goods (ARTG) rather than registered.[8] When a complementary medicine is listed on the ARTG, the therapeutic indications are not evaluated by the regulatory body, the Therapeutic Goods Administration (TGA) at the time of listing. However, at the time of listing, the sponsors are required to certify that they hold the evidence to support indications and claims made for their medicine and that this information be made available to the TGA upon request. Furthermore, there is no requirement for a complementary medicine to be listed or registered in Australia.

Hence the impact of the CAMs consumed by cancer patients need to be considered under these significant caveats. It would be ideal to recommend patients to cease all CAM whilst undertaking all active therapy for their malignancy – however the compliance of this would be extremely variable. A 2014 study by Thakerar, et al found that 2% of patients at a tertiary cancer institution chose not to follow pharmacist recommendations relating to the discontinuation of CAM due to safety issues.[2]

Whilst this paper focuses on the potential problems or interactions associated with CAM when used in combination with conventional cancer therapies, it is acknowledged that some CAM may have possible beneficial effects in cancer patients.[9] As recommended in The Society of Integrative Oncology (SIO) guidelines for integrative oncology, our service recommends all cancer patients considering the use of CAM, have a two way conversation with a trained healthcare professional before commencing and discuss realistic expectations and potential risks and benefits.[10] Realising that there will be patients who will consume CAMs despite the above, either through their own volition or advice of outside "practitioners", based on the current literature and based on the CAMs that generated enquiries through our service, general recommendations below are provided to them by our service if they wish to commence or continue with their CAM.

Safety

One of the major issues with these agents is safety, which needs to be assessed from the reported literature, optimally from prospective trials or at least theoretically gleaned from known possible interactions or experimental data. For example, the consumption of green tea has been associated with several cases of hepatitis,[11-14] possibly caused by active constituent, epigallocatechin-3-gallate or its metabolites, which under particular conditions related to the patient's metabolism, can induce oxidative stress in the liver [13]. Therefore, patients with hepatic dysfunction should consume green tea with extreme caution and monitoring of liver function tests may be warranted. In some situations, where the data suggests a CAM is potentially unsafe, patients should be advised in the strongest manner to avoid taking this CAM altogether, whether undergoing treatment for cancer or not.

Interactions

There are several mechanisms by which a CAM may interact with a chemotherapy medication. Firstly, a CAM may be a substrate, inhibitor or inducer of drug metabolism or drug transport in the liver, intestine or kidney, including the cytochrome P450 (CYP) isoenzymes, uridine diphospho-glucuronosyl transferases (UGT) or membrane transporters such as ABC-B1, also known as P-gp, etc. For example, turmeric has been shown to inhibit intestinal ABC-B1, CYP 1A1, 1A2 and 3A4 and induce CYP 2A6 isoenzymes.[15-21] Doxorubicin is a major substrate of CYP 3A4, CYP 2D6, and ABC-B1.[22] The inhibitory effect of turmeric on CYP 3A4 and ABC-B1 may increase serum levels of doxorubicin increasing the risk of toxicity. Another example is cyclophosphamide which is a pro-drug converted to its active form, 4-OH cyclophosphamide, via CYP 2B6, 2C9 and 3A4 isoenzymes.[22] The inhibitory effect of turmeric on CYP 3A4 may reduce plasma levels of the active form of cyclophosphamide and thus decrease the anti-tumour action of cyclophosphamide.

As stated above, the doses required for these interactions to be clinically significant are poorly defined. It appears prudent that for potential interactions via this mechanism, we advise patients to avoid the CAM for at least 48 hours prior to commencement of chemotherapy until 48 hours post the completion of chemotherapy. However, 48 hours is the arbitrary pragmatic time used at our centre, though both medications and CAM have different half-lives. It would be optimally more appropriate to consider the half-life of both the medications and CAM in question and avoid the CAM for at least 5 times the longest half-life. Nevertheless, a limitation to this method is the severe paucity of data regarding CAM pharmacokinetics.

Secondly, at the level of drug absorption interactions can also occur. For example, intravenous administration of licorice can uncommonly cause diarrhoea[6] and thus may theoretically reduce the absorption of other oral medications when taken concurrently.[6] In this situation, it is advised that the administration of oral medications occurs at least an hour before, or two hours after the administration of CAM that may interfere with drug absorption.

Interactions via other mechanisms are also possible. Fish oil has been shown to contain substantial levels of platinum-induced fatty acid (PIFA) 16:4(n-3), which has been shown to induce resistance to chemotherapy in preclinical mouse models.[23] A recent preclinical study in mice found that fish oil increased tumour volume by an estimated 142.4 mm^3, 166.3 mm^3 and 147.1 mm^3 for cisplatin, irinotecan and oxaliplatin, respectively.[23] Based on these findings, the investigators advise fish oil is avoided from the day prior to commencement of chemotherapy until the day after completion of chemotherapy.[23]

Preliminary in vitro and in vivo data shows that green tea polyphenols are antagonist with bortezomib and other boronic acid-based proteasome inhibitors. The former blocks the proteasome inhibitory effects of the latter, leading to reduced cell apoptosis.[24] The concentrations of the most active constituent of green tea, epigallocatechin gallate (EGCG) studied are consistent with those achieved in the blood of humans ingesting green tea.[24] Therefore, green tea should be avoided by patients being treated with bortezomib.

Antioxidants

Some CAM such as milk thistle and green tea possess antioxidant activity.[25-27] The use of antioxidants in combination with radiotherapy and chemotherapy agents that generate free radicals remains controversial.[28] Some data suggest antioxidants may reduce treatment-related adverse effects of radiotherapy and chemotherapy and other data suggest antioxidants protect both tumour cells and healthy cells from oxidative damage generated by radiation therapy and some chemotherapy agents, and thus may possibly result in tumour protection.[28] Chemotherapy agents that generate free radicals include the alkylating and alkylating-like agents,eg. cisplatin, carboplatin, chlorambucil, carmustine, cyclophosphamide, busulfan, ifosfamide, anthracyclines,eg. doxorubicin, daunorubicin, epirubicin, and podophyllotoxin agents, eg. etoposide and teniposide.
Our general advice regarding CAM with antioxidant activity is to avoid them for at least 48 hours pre chemotherapy agents that generate free radicals and radiotherapy, until 48 hours post treatment. Nevertheless, as stated above a limitation to this recommendation is the severe paucity of data regarding CAM pharmacokinetics,

and similarly mechanistic studies assessing the time profile of the interaction between antioxidants and treatment-induced radicals.

Antiplatelet effects

CAM with antiplatelet effects including ginger, turmeric and high doses of fish oil and reishi mushroom may increase the risk of bleeding in patients who are thrombocytopenic, undergoing surgery, or taking concomitant anticoagulants.[29-37] Consider turmeric, in which the major active constituents are curcuminoids, mainly curcumin.[6] Preliminary research suggests curcumin might inhibit platelet-activating factor and arachidonic acid platelet aggregation, possibly interfering with thromboxane synthesis and thus decreasing platelet aggregation.[29, 30] It is often difficult to establish the clinical significance of these effects in the haematology/oncology setting due to the lack of human data.

The effect of some CAM on platelet aggregation is unclear. For example, in healthy humans, a reishi mushroom dose of 3g per day has been shown to reduce platelet aggregation,[37] however a dose of 1.5g daily did not affect platelet aggregation [33] therefore there may be a dose relationship. We advise that CAM with anticoagulant properties are ceased 2 weeks prior to surgery and are avoided in patients who are thrombocytopenic or bleeding. They should be used with extreme caution in patients taking concomitant anticoagulants.

Immunomodulatory effects

Some CAM have immunostimulatory or immunosuppressive effects and thus may interfere with the efficacy and/or toxicity of immunosuppressive therapy such as chemotherapy and immunotherapy agents such as ipilimumab and immune checkpoint inhibitors such as PD1 antagonists. Astragalus has demonstrated immunostimulatory effects in in vitro and in vivo.[38-40] In mice, the polysaccharide constituents of astragalus appear to bind and activate B cells and macrophages.[39] Other in vitro and in vivo research has found that astragalus may increase the activity, and/or number of T cells.[38, 40]

We advise that CAM with immunomodulatory properties are avoided for 48 hours pre and post immunosuppressive agents such as chemotherapy and are avoided altogether by patients being treated with immunotherapy agents.

Estrogenic effects

There are CAM including turmeric, milk thistle, licorice and astragalus are thought to have estrogenic effects [41-50] and should be avoided altogether by patients with hormone sensitive cancers and conditions such as breast cancer, ovarian cancer and endometriosis. Animal data suggest silymarin, a constituent of milk thistle can bind to estrogen receptors and therefore may theoretically have estrogenic effects.[46]

Preliminary data suggest estrogenic activity may sometimes be concentration dependent as with the major constituent of licorice, glabridin, which appears to have an estrogen receptor-dependent, growth-promoting effect at low concentrations and estrogen receptor-independent antiproliferative activity at higher concentrations.[41] Furthermore, due to lack of data, the extent of estrogenic activity and the mechanism for such activity is often unknown making it difficult to establish the clinical significance of potential effects.

Conclusion

Cancer patients do consider the use or actually consume CAM during their cancer therapy. Whilst many CAM may be considered "safe" when taken by themselves, even with lack of high level data, there is theoretically, a potential for interactions (at PK/PD level) or an increased risk of serious adverse effects when taken concurrently with conventional anticancer therapies such as chemotherapy and/or radiotherapy, or when taken pre-surgery. The end result may be either increased toxicity from the cancer therapy, or on the other hand reduced treatment efficacy. These aspects have been highlighted by the review of CAM enquiries made to a tertiary cancer centre Medicine Information Service over a 2 year period and a literature review of the 10 most frequent CAM that generated the enquiry. Human studies and high level evidence are both severely lacking in this area and potential drug interactions often need to be implied/predicted using in vitro data or in vivo animal data, making it difficult to quantify the clinical significance. Similarly the quality control of the CAM preparations is also suspect and unregulated in most circumstances. It would be thus ideal to recommend patients to cease all CAMs whilst undertaking all active therapy for their malignancy – however the compliance of this would be extremely variable. Realising that there will be patients that will consume CAMs despite the above, general advice can be provided to them if they wish to commence or continue with their CAM.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Table 1. Number of CAM products and compounds per enquiry

Number of CAM per enquiry	Number of enquiries (%)
Products	
1	194 (42%)
2–5	189 (41%)
6–10	62 (13%)
>10	17 (4%)
Compounds	
1	145 (31%)
2–5	145 (31%)
6–10	74 (16%)
>10	98 (21%)

Table 2. Patient demographics

Patient demographics	*n* (%)
Sex	
Female	231 (50%)
Male	139 (30%)
Unknown	92 (20%)
Age (years)	
0–20	0 (0%)
21–40	55 (12%)
41–60	179 (39%)
61–80	126 (27%)
81–100	5 (1%)
Unknown	97 (21%)
Existing/newly diagnosed cancer	
Existing	209 (45%)
Newly diagnosed	158 (34%)
Unknown	95 (21%)
Therapy intent	
Adjuvant	264 (57%)
Palliative	103 (22%)
Unknown	95 (21%)
Treatment modality	
Anticancer agent (chemotherapy, immunotherapy and targeted therapy)	210 (45%)
Radiotherapy	44 (10%)
Anticancer agent combined with radiotherapy	67 (15%)

Surgery	3 (1%)
Anticancer agent combined with surgery	12 (3%)
Nonanticancer medication	33 (7%)
Other	10 (2%)
Unknown	86 (19%)

Table 3. Summary of interactions/problems associated with the top 10 CAMs

CAM	Drug interactions	Antioxidant activity	Antiplatelet activity	Other
Fish oil	May decrease activity of chemotherapy†	Nil	At doses >3 g/day†	Possible immunostimulatory effects at doses >3 g/day†
Turmeric	Inhibits P-gp†‡ Inhibits CYP 1A1†‡ Inhibits CYP 1A2†‡ Inhibits CYP 3A4†‡ Induces CYP 2A6†	Yes†‡	Yes†‡	Possible immunostimulatory effects† ?Estrogenic effects‡ ?Antiestrogenic effects‡
Coenzyme Q10	Nil	Yes†	Nil	Possible immunostimulatory effects†
Milk thistle	Inhibits UGT‡ Inhibits P-gp† ?Inhibits CYP 2C9†‡ ?Inhibits CYP 3A4‡	Yes†‡	Nil	Estrogenic effects†
Green tea	Inhibits UGT†‡ Inhibits OATP 1A2†‡ Inhibits OATP 1B1†‡ Inhibits OATP 2B1†‡ ?Inhibits CYP 3A4 (intestinal)†‡ ?Induces CYP 3A4 (hepatic)†	Yes†‡	Not reported in humans‡	Inhibits therapeutic effect of bortezomib†‡ Linked to several cases of hepatotoxicity†
Ginger	Increases tacrolimus levels‡ Decreases cyclosporin levels†	Yes†‡	Yes†‡	Nil
Lactobacillus	Nil	Nil	Nil	Risk of pathogenic colonization in immunocompromised patients†
Licorice	Inhibits P-gp‡ Inhibits CYP 2B6‡ Inhibits CYP 2C9‡ ?Inhibits CYP 3A4‡ Induces CYP 2C9† ?Induces CYP 3A4†	Yes†‡	Nil	?Estrogenic effects†‡ ?Antiestrogenic effects‡†

	?Reduces effects of cisplatin†			
Astragalus	Nil	Yes‡	Nil	Immunostimulatory effects†‡ Estrogenic effects‡
Reishi mushroom	Inhibits CYP 1A2† Inhibits CYP 2E1† Inhibits CYP 3A4†	Yes‡	High doses†	Possible immunostimulatory effects† Possible immunosuppressive effects‡

‡In vitro.

†In vivo (animal/human).

CYP, cytochrome P450; P-gp, P-glycoprotein (also known as ABC-B1); UGT, uridine 5-diphospho-glucuronosyltransferase; OATP, organic anion-transporting polypetide.

Note: Fully referenced copy of Table 3 is available as Supplementary Document 1.

Figure 1. CAM enquiries per cancer type.

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