Grapefruit juice and St John's Wort are just the tip of the iceberg

How can we prevent damaging interactions in this era of long-term oral cancer therapies?

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Certain foods, prescription drugs and complementary remedies interact with cancer therapies, altering the effective dose and putting patients at risk. Yet there is scant clinical evidence on which interactions are dangerous, and many doctors are unaware of what their patients may be taking. Calls are now growing for a strategy to get to grips with this hidden problem.

One of the biggest hurdles in bringing a new cancer drug to market is turning a promising molecule into something that actually works therapeutically in the human body. The active compound has to be absorbed by the body and reach the parts that matter so that it acts before it is flushed from the system or broken down in a way that deprives it of its cancer fighting properties. The drug has to be effective at strengths that don't put a patient's life and long-term health at risk from heart failure, stroke, or attacks on the liver or other organs. Tolerability is also important, particularly for long-term therapies – no patient wants a life blighted by diarrhoea, vomiting or a facial acneiform rash.

If cancer patients were more aware of the delicate balance, they might think twice before casually reaching for a new health supplement from their local supermarket, or embarking on a course of an additional prescription medicine that could radically alter the way their body deals with their cancer drugs.

If doctors, nurses and pharmacists were more alert to the possibilities, they might make more effort to ask what other substances their cancer patients might be taking that could interact with their therapy, and be quicker to explore interaction as a possible factor if patients fail to respond to a drug or experience unexpected side-effects.

It has long been known that medicines can interact with other prescription drugs, with complementary/alternative medicines (CAM), or even with certain items of food or drink. But this poses particular problems for cancer patients – problems that are likely to get worse as new agents come onto the market, and as management of the disease moves towards long-term control with oral therapies.

Because of the toxic nature of many cancer drugs, interactions that increase the amount of the active drug circulating in the body can have fatal consequences. Even where the consequences are less dramatic, if they are not properly explored, they can lead to patients being taken off a beneficial drug on the grounds that they are 'intolerant'.

Interactions that lower the level of active drug in the body, on the other hand, render the therapy less effective. Again, without proper investigation, it can be easy to assume the patient is just one of the unlucky ones whose disease is resist-

ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

ant to the therapy. The problem is particularly acute with adjuvant treatments, where evidence of response or resistance may not become apparent for many years.

How serious is this problem?

The behaviour of cytochrome P450 3A4 (CYP3A4) offers a useful starting point for exploring the significance of the interaction problem. This enzyme plays a greater or lesser role in metabolising the tyrosine kinase inhibitors (TKIs) dasatinib (Sprycel), erlotinib (Tarceva), gefitinib (Iressa), imatinib (Glivec), lapatinib (Tyverb), nilotinib (Tasigna), sorafenib (Nexavar) and sunitinib (Sutent), and indeed some non-TKI anti-cancer drugs such as docetaxel, irinotecan, taxol, vincristine, etoposide, ifosfamide and tamoxifen.

If a patient's CYP3A4 levels increase above the range considered normal, these drugs are likely to be broken down into inactive compounds and flushed from the system too quickly, giving them less chance to do their anti-cancer work – effectively an underdose. If levels of the same enzyme are too low, however, more of the drug remains active in the body for longer than intended – effectively an overdose that could lead to very serious side-effects.

CYP3A4 levels seem to be affected by a wide spectrum of substances. The United States National Library of Medicine lists 38 prescription drugs – including antifungals, antibiotics and antidepressants – that inhibit CYP3A4 (making the cancer drug more toxic). It lists a further 20 drugs that induce CYP3A4 (reducing the efficacy of the cancer drug). Added to this are many CAM products and common foods known or suspected to interact with the enzyme – including grapefruit, starfruit, St John's Wort, kava-kava, cat's claw, valerian root, milk thistle, goldenseal, black cohosh, many herbal teas, ginseng, and genistein (found in soy products). The potential for problems is clear.

Some of these interactions pose a very serious threat (see table overleaf). The antifungal drug ketoconazole, for instance, can lead to a five-fold increase in serum concentrations of dasatinib, and a three-fold increase with nilotinib and lapatinib. While serum concentrations of many of the TKIs are reduced by more than 80% in the presence of the bactericidal antibiotic rifampin. St John's Wort, known as the 'sunshine herb', and commonly used in many countries as a natural remedy to treat insomnia, sadness and depression, is known to reduce serum concentrations of imatinib by 30%, and is likely to have a similar effect in other TKIs.

Interactions that are flagged up as potentially dangerous by preclinical pharmacological data do not always play out in the clinic, however, as can be seen from the clinical data on sorafenib (see table), where ketoconazole shows no effect on serum concentration levels. It is therefore difficult to tell which of the substances featured on lists of inhibitors or inducers actually do pose a danger for

which cancer drugs, as only a minority have been studied in a clinical setting. Indeed, many potential interactions would be unlikely to occur in practice – perhaps because the interacting drug is taken at a different time of day, or prescribed for too short a time, or the dose is too low to have a serious impact.

More of a worry, perhaps, are the hundreds of non-prescription products that cancer patients take of their own volition and that have never been subjected to pharmacological scrutiny.

How widespread is this problem?

Drug interactions cannot always be avoided, but so long as they are identified, they can at least be managed. The danger lies in interactions that are not being identified, and by their very nature it is difficult to know how widely this is happening.

Research by Molassiotis et al. (*Ann Oncol* 16:655-663) showed that around 35% of Europe's cancer patients use some form of CAM, with rates in some countries as high as 73%. Not every CAM is biologically active, but a lot are, and very little is known about how these products may interact with cancer medication. Molassiotis found that herbal medicine was the most used CAM in the majority of countries and was in the top five CAM types used in every country bar one. Megavitamins/vitamins/minerals, homeopathy, and medicinal teas were also all in the top five in at least half of the countries surveyed.

Studies confirm what is already well known among patient advocacy groups – that doctors are often unaware of what additional substances their patients are taking. They seldom ask and patients can be reluctant to reveal the information, perhaps for fear of being ridiculed or told to stop, or simply because they don't perceive 'natural' remedies as relevant.

There is less excuse for such communication failures with prescription medicines. General practitioners wanting to prescribe an antibiotic will usually ask their patients if they are taking any other prescription medicines and in most cases they know if their patient is being treated for cancer. Community pharmacists who provide the antibiotics should be aware of what other prescription drugs that patient is taking. However, they may not, if those drugs are delivered by the hospital, which is usually the case with chemotherapy and, in many countries, with oral cancer therapies.

In the absence of computerised medical records and automatic interaction alerts, the system relies on professional vigilance, and there are many opportunities for potential problems to be overlooked.

A study of the literature on the frequency of drug–drug interactions (DDIs) in cancer published in the *Annals of Oncology* last year (vol 20, pp1907–1912), found

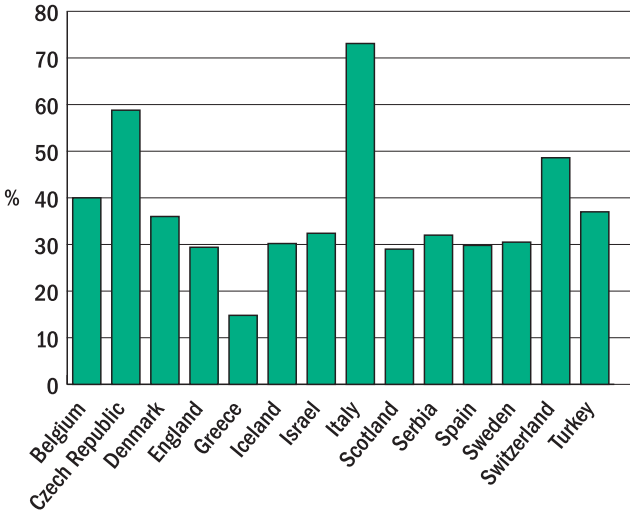
SOME INTERACTIONS CAN HAVE A MAJOR IMPACT

Object Drug	Inhibitor	Inducer	Comments
Dasatinib	Ketoconazole		5-fold ↑ AUC
		Rifampin	>80% ↓ AUC
Erlotinib	Ketoconazole		>85% ↑ AUC
		Rifampin	>80% ↓ AUC
		Smoking	Smokers have 65% lower AUC than nonsmokers
Gefitinib	Itraconazole		60%–80% ↑ AUC
		Rifampin	>80% ↓ AUC
Imatinib	Ketoconazole		80% ↑ AUC
		Rifampin	75% ↓ AUC
		St John's Wort	30% ↓ AUC
Lapatinib	Ketoconazole		3.6-fold ↓ AUC
		Carbamazepine	75% ↓ AUC
Nilotinib	Ketoconazole		3-fold ↑ AUC
		Rifampin	80% ↓ AUC
Pazopanib	Ketoconazole		3-fold ↑ AUC of pazopanib eye drops
Sorafenib	Ketoconazole		No change in AUC
		Rifampin	37% ↓ AUC
Sunitinib	Ketoconazole		50% ↓ AUC
		Rifampin	45% ↓ AUC

AUC – area under the curve (effective concentration of the drug)

Source: J Horn and Philip Hansten, *Pharmacy Times* April 2010 (http://www.pharmacytimes.com/issue/pharmacy/2010/April2010/DrugInteractions-0410)

Use of CAM in cancer across Europe



Around 35% of Europe's cancer patients are thought to use some type of CAM – much of it biologically active. Herbal medicine was in the top five most popular types of CAM in every country surveyed bar one. Megavitamins/vitamins/minerals, homeopathy, and medicinal teas were in the top five in at least half of the countries

Source: Molassiotis et al. (2005) *Ann Oncol* 16:655–663

only eight publications, six of which reported on potential interactions, with only two trying to estimate the frequency of actual interactions. It concluded that "although it seems that one-third of cancer outpatients are at risk of DDI, the proportion of them who actually suffer from DDIs remains unknown." They advise caution, in particular, in prescribing warfarin, anticonvulsants and antihypertensives.

Warnings have also been sounded about the risk of interactions between tamoxifen and antidepressants. Estimates (Horn and Hansten, *Pharmacy Times*, March 2009) suggest that almost a third of patients on tamoxifen are taking antidepressants. But many antidepressants – particularly fluoxetine (Prozac), paroxetine (Paxil), bupropion (Wellbutrin) and duloxetine (Cymbalta) – are known to significantly inhibit the enzyme CYP2D6, which is needed to make tamoxifen do its job.

A recent retrospective clinical study did not find evidence that all these drugs reduced the effectiveness of tamoxifen in clinical practice, but it did find almost double the risk of death (91% increase) among women taking paroxetine for at least 75% of the time they were on tamoxifen. Excess mortality was reduced to 24% increased risk if the overlap was only for 25% of their time on tamoxifen (Kelly et al. 2010, *BMJ* 340:c693).

It is difficult to know how many of the doctors who prescribe antidepressants, the pharmacists who administer them and the breast cancer patients who take them are aware of these dangers. There is anecdotal evidence that awareness is not as high as it should be even among psycho-oncologists. And while some breast cancer advocacy organisations such as Mamazone in Germany cover this issue in their national and regional education days and provide information and advice on their website, the UK advocacy organisation Breast Cancer Care makes no mention of it in their patient leaflet on tamoxifen, and nor does the website of the Macmillan Cancer Support.

A GROWING CONCERN

Jutta Hübner, a medical oncologist specialising in the use of CAM, who heads the department of Palliative, Supportive and Complementary Therapy at the University Cancer Centre in Frankfurt, is reluctant to hazard a guess at the scale of the interaction problems among cancer patients. She is convinced, however, that it is steadily growing. "The problem with TKIs and drugs like that is they are for the long term. Chemotherapy lasts for about three months, and in most cases it is only the day of therapy itself that is the really sensitive period. TKIs, or even oral chemotherapy, is something patients take at home, so the possibility of interactions is much greater."

She points to the steady rise in the number of CAM substances now available on the Internet, including a lot of traditional Chinese and Ayurvedic medicines which are often biologically highly active, but in ways that have never been pharmacologically investigated. Compounding the effects of this rise in supply is a parallel rise in demand, with the trend for patients to want to know more and take more personal responsibility for their own health. "Our patients learn that they have to look for themselves in the system. And when you look for yourself, you find some things that are good and some things that are problematic. It is very hard for the patients to know which way to go."

Hübner offers a couple of examples from her own recent experience to illustrate how various and unpredictable are the potential problems. One patient on chemotherapy had come in after suffering very serious side-effects. It turned out that she had been drinking her own urine, having read that this could help fight the cancer. As her urine contained large quantities of the metabolites of the chemotherapy drug that had been flushed from her system, she was in effect giving herself a second dose.

Another patient who had been doing very well on chemotherapy recently turned up at clinic, also suffering very serious side-effects. This wasn't a problem with interaction. It was simply that since starting a 'cancer diet', she had lost so much weight that the chemotherapy dose she had started on

"Some things are good and some things are problematic – it is very hard for patients to know which way to go"

was now too big for her reduced body mass, and the change had gone unnoticed. Hübner says, "She could have had very, very serious consequences, but fortunately they stopped the chemotherapy. This is an example that shows we really should be careful to ask our patients what they are doing." .

Doctors are aware that interactions can be a problem, she adds, but they don't really know what to look for. "Most of our data about interactions are derived from preclinical experiments in laboratories and animal experiments, whereas most interactions that really happen are not reported." She worries that there is too much hype around some of the pharmacological data on interactions, and cites the recent flurry of articles around green tea and bortezomib (Velcade) as a case in point.

"There are pretty few data, and I've had so much discussion with patients: 'Can we drink one cup of green tea a day or not?' I think we need to calm down. There is even a new paper saying green tea extract and Velcade go very well together." If you create too much hype over very uncertain data, you end up with a confused picture that can make life very stressful for patients and very difficult for oncologists when they are asked for advice.

"The question always for a doctor is what to tell the patients. We can't say, 'Don't use all these things', because, using the example of green tea and Velcade, the problem is not just green tea; any antioxidant will do exactly the same. So if you want to say 'no green tea', you also have to tell the patient: 'Don't eat any fruit, don't drink any tea, drink water and eat bread and that's all.'" Which, as she points out, is pretty much the advice some patients are given. "I have seen some sheets for patients telling them what they should not eat, and sometimes I'm asking, 'For heavens sake what do you eat if you have to be careful of all these things?'"

Hübner, who chairs the CAM working party of the German Cancer Society (Deutsche Krebsgesellschaft), wants to see a whole new approach to dealing with this issue, based on:

- regular communication with patients
- a more open-minded approach to CAM, based on seeking expert advice rather than always advising against, and
- a systematic effort to build up an evidence base about which substances present significant interaction problems with which therapies in clinical practice.

With her colleagues on the CAM working party, she is recommending the use of a questionnaire that could be used in outpatient clinics and hospitals to regularly screen patients about what they are doing. This would be backed up by an expert advice centre that doctors could turn to for advice on interactions, This would allow the patient to 'own up' to taking something without feeling they will be punished by their oncologist.

They also want to set up a register where doctors can report interactions or unexpected side-effects, in order to compile information and to allow doctors to swap notes with colleagues elsewhere whose patients are taking similar compounds.

Hübner herself has been arguing for many years about the need for guidelines on CAM, including simple and clinically relevant information on interactions, to replace the current reliance on lengthy lists of hypothetical dangers. This would be helpful for doctors and for pharmacists, she suggests, but also for patients, many of whom are currently well aware of the dangers of interactions, but hazy on details. "Nearly everyone seems to have heard of St John's Wort and grapefruit," she says, "but often they assume that if they stay away from these two products then everything else is OK."

As so often happens, however, the clinical studies needed to draw up these guidelines and develop knowledge and expertise in this area are being held up by lack of funding. "We have many interesting projects, but no funding. We are waiting for a response from the Deutsche Krebshilfe, (German Cancer Aid) which gives support to research, and I am talking to many other people who may give some money to some of our projects. This is a big difference to the US system where the cancer centres get public funding for their complementary activities as well."

A role for pharmacists

Hübner and her colleagues can expect support for their efforts from one key group of professionals, who 10 years ago joined together to form the European Society of Oncology Pharmacy. ESOP believes oncology pharmacists are perfectly positioned to play a key role in communicating with patients about interactions, side-effects and adherence, as the trend towards long-term oral therapies reduces the contact

between patients and their cancer clinic.

At a European level they are still trying to identify the role currently played by ESOP members in their contact with cancer patients in different countries, to which end they conducted a survey, published last year in the *European Journal of Oncology Pharmacy* (vol 3, p 25). This asked a number of general questions, but also looked specifically at how well equipped they are to advise patients with CML (chronic myeloid leukaemia) – a particularly relevant group because of the long-term nature of their treatment and the variety of oral therapies.

At the same time, ESOP's German affiliate is forging ahead with proposals designed to significantly step up the contribution pharmacies play in the long-term management of cancer patients. If successful, it could provide a template that could be adjusted for use elsewhere.

These proposals seek to:

- Ensure every patient on oral cancer therapies receives accurate, relevant and concise information
- Provide for regular consultations where the pharmacists get feedback on side-effects, adherence and about what else the patient is doing that might affect their therapy, and can offer advice

Klaus Meier, the president of ESOP, has been at the forefront of developing and pushing forward these proposals on behalf of its German affiliate, the Deutsche Gesellschaft für Onkologische Pharmazie (DGOP). Like Hübner, he feels the currently available interaction lists are of little use in advising patients, and together with the German Cancer Society, the DGOP has started consulting with pharmaceutical companies and others with a view to drawing up patient-friendly leaflets for use in pharmacies.

"If you tell patients 20 topics, they will have forgotten 18 when they leave," says Meier. "We want to focus on just, for instance, the three main drugs and the three main non-prescription drugs with which it will not work. We will choose those that do the main harm, and those that may not be quite so harmful, but are most widely used."

This would be supplemented by a questionnaire. Part would be filled out by the patient at home, to record for instance when they take their drug and what side-effects they experience. The rest would be filled in at a monthly consultation with the pharmacist, including a question about what else the patient is using to promote their health. Such a system would allow pharmacists to individualise their advice, says Meier. "We want to know what really is going on with the patient, and not just fill them up with general stuff. What really is the problem?"

If successful, such procedures should not only help improve patient outcomes, but could also provide a goldmine of information on adherence, side-effects, what CAM patients are using, and symptomatic interactions. But Meier knows that getting pharmacies to expand their role in this way will be neither cheap nor easy. As a means of enforcement, the DGOP is actually proposing to extend to all oral cancer drugs the conditions demanded by the European regulatory body, EMEA, for the administration of thalidomide – the drug that caused a wave of birth deformities when it was first introduced in the 1960s, which was recently given approval for use in patients with multiple myeloma. Should these proposals be accepted, both doctors and pharmacists would be required to sign on the prescription for any oral cancer medicine that they have given key information to their patients and asked certain mandatory questions.

"There's also the question of financial support, if you ask pharmacists to have more time and space in their pharmacy for private consultations," adds Meier – not to mention the cost of the additional training, which the DGOP has already started, with a series of courses running across Germany's 16 regions.

German pharmacies are under pressure in today's cost-conscious environment to justify the monopoly position they hold, and this may be part of the motivation behind the DGOP's bid to step up the value-added they can offer for cancer patients. But it is hard to deny the need for the sort of systematic, individualised and informed follow-up of patients on oral therapies that they are proposing, whether this is done in pharmacies, or in out-patient clinics, as Hübner suggests, or by cancer nurses over the phone.

Meier argues that you not only benefit from a reduction in the likelihood of potentially fatal interactions, but also maximise the value for money from very expensive cancer drugs. With some oral therapies costing tens of thousands of euros per patient per year, it would surely be worth a little investment to ensure that their effects are not largely wiped out by a bottle of sunshine herb purchased at €12.95 from the local corner shop.

"We want to know what is really going on with the patient, not just fill them up with general stuff"