L’importanza dell’aderenza terapeutica nelle terapie oncoematologiche per via orale

VALUTARE E AFFRONTARE IL RISCHIO DI TOSSICITA' E DI INTERAZIONI FARMACOLOGICHE

Torino, 20 dicembre 2017

M. Scaldaferri

Il contesto...

- Progressiva disponibilità di farmaci con meccanismi d'azione innovativi e profili di tossicità con aspetti nuovi
- Procedure autorizzative rapide e studi di non inferiorità
- Scarsa conoscenza della tossicità a lungo termine
- Caratteristiche dei pazienti della pratica clinica spesso differenti da quelle degli studi
- Importanza della qualità della vita

Il contesto...

Due elementi fondamentali:

- La complessità del paziente oncologico:

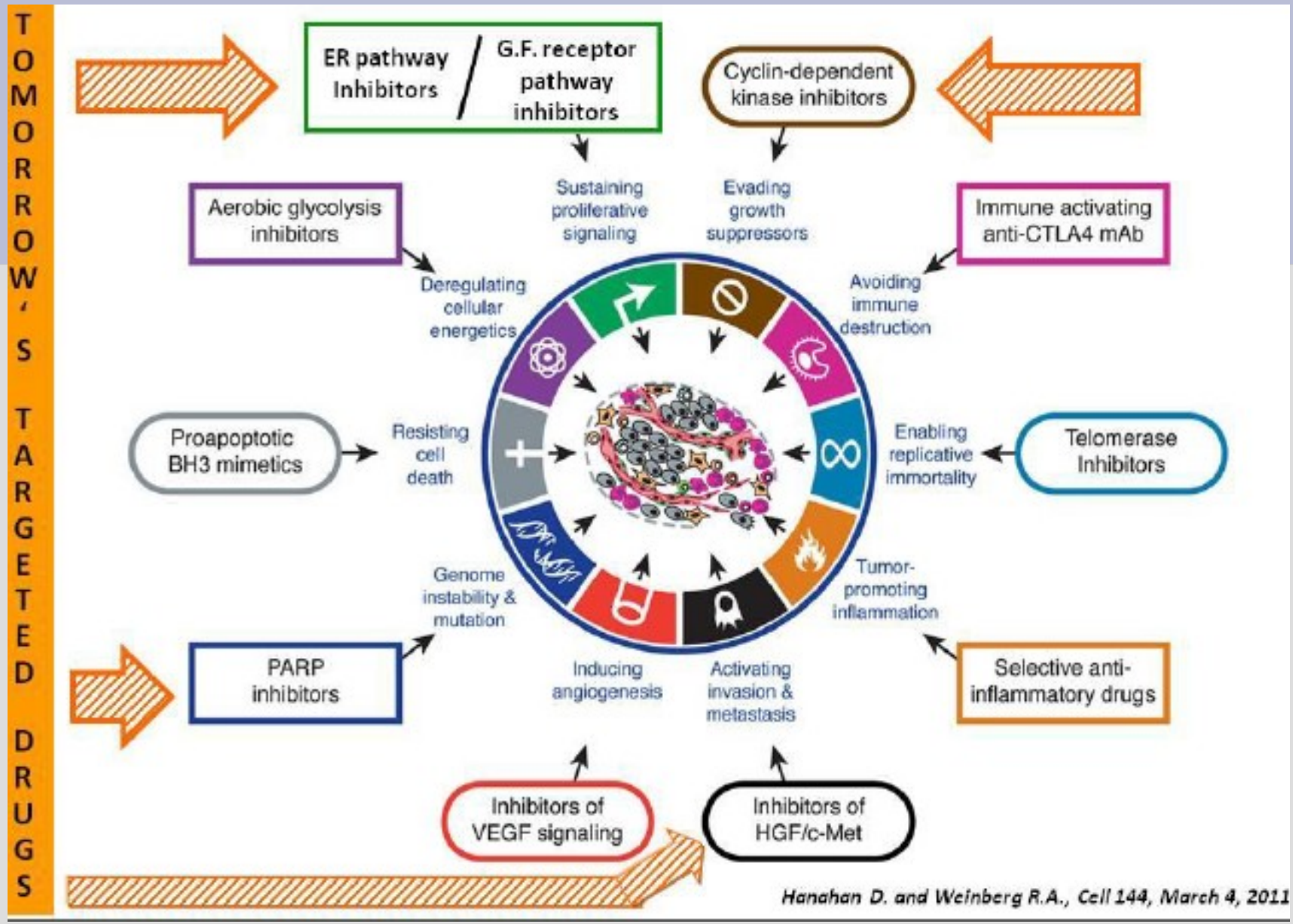
  - caratteristiche spesso diverse dalla popolazione degli studi

  - età

  - comorbidità / multimorbidità

  - contesto sociale ed atteggiamento nei confronti della malattia oncologica

- La politerapia “in senso lato”



Effetti “on target”

Effetti “off target”

Complicanze correlate alla terapia oncologica

- Ipokalemia, Ipomagnesemia, Ipocalcemia
- Disfunzione epatica e renale
- Nausea, vomito, diarrea
- Scarso controllo glicemico
- deidratazione, denutrizione

Heart - Tyrosine-Kinase Proteins

- ABL: protection from oxidative stress
- KIT: remodelling after miocardial infarction
- FAK1: physiologic cardiac hypertrophy
- RAF1: protection from oxidative stress and arterial hypertension
- JAK/STAT: anti-apoptotic effect, regulation of miocardial capillarity density
- RSK: anti-apoptotic effect
- mTOR: upregulation of HIF (hypoxia inducible factors), including VEGFR

CHEMIOTERAPICI CHE POSSONO DETERMINARE UN QT LUNGO

Histone deacetylase inhibitors
Vorinostat

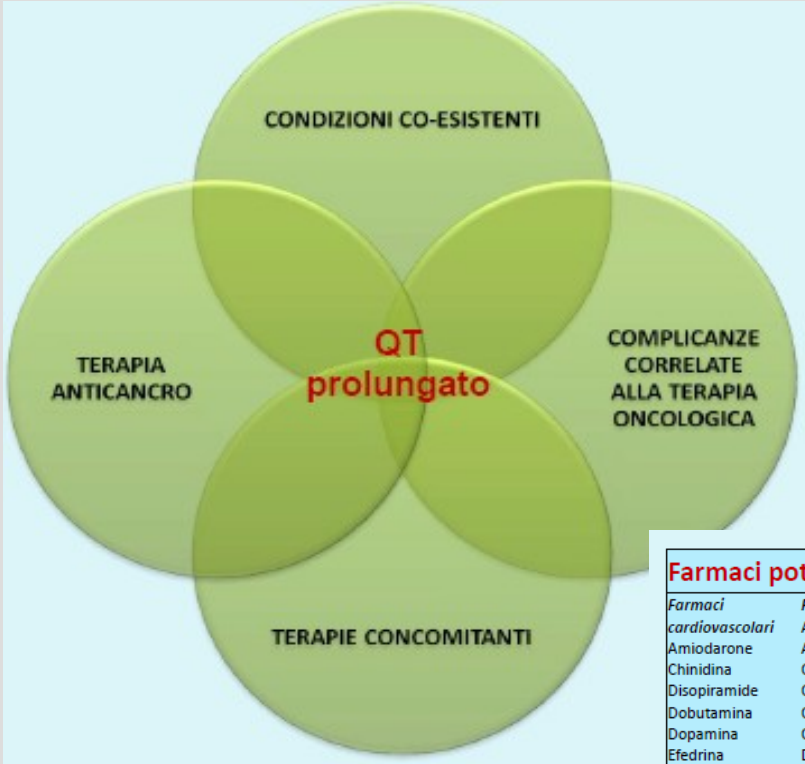
Multitargeted tyrosine kinase inhibitors
Sunitinib
soranefib

BCR-ABL inhibitors
Dasatinib
Nilotinib
Vantenanib

ErbB-1/-2 receptors inhibitors
Lapatinib

Proteasome inhibitors
Bortezomib

Miscellaneous
Arsenic trioxide



Farmaci potenzialmente a rischio di prolungare l'intervallo QT.

Farmaci cardiovascolari
Amiodarone
Chinidina
Disopiramide
Dobutamina
Dopamina
Efedrina
Epinefrina
Flecainide
Ibutilide
Indapamide
Isradipina
Midodrina
Norepinefrina
Sotalolo

Farmaci SNC
Aloperidolo
Amitriptilina
Citalopram
Cloralio idrato
Clorpromazina
Clomipramina
Droperidolo
Felbamato
Fluoxetina
Galantamina
Imipramina
Levomepromazina
Litio
Metadone
Metilfenidato
Nortriptilina
Olanzapina
Paroxetina
Quetiapina
Risperidone
Sertindolo
Sertralina
Tioridazina
Tizanidina
Trimipramina
Venlafaxina

Farmaci GI
Dolasetron
Domperidone
Granisetron
Ondansetron

Farmaci respiratorio
Salbutamolo
Salmeterolo
Terbutalina

Farmaci antibatterici
Azitromicina
Ciprofloxacina
Claritromicina
Eritromicina
Levofloxacina
Moxifloxacina
Ofloxacina
Cotrimossazolo

Farmaci antivirali
Amantidina
Foscarnet

Farmaci antiparassitari
Clorochina
Meflochina
Pentamidina

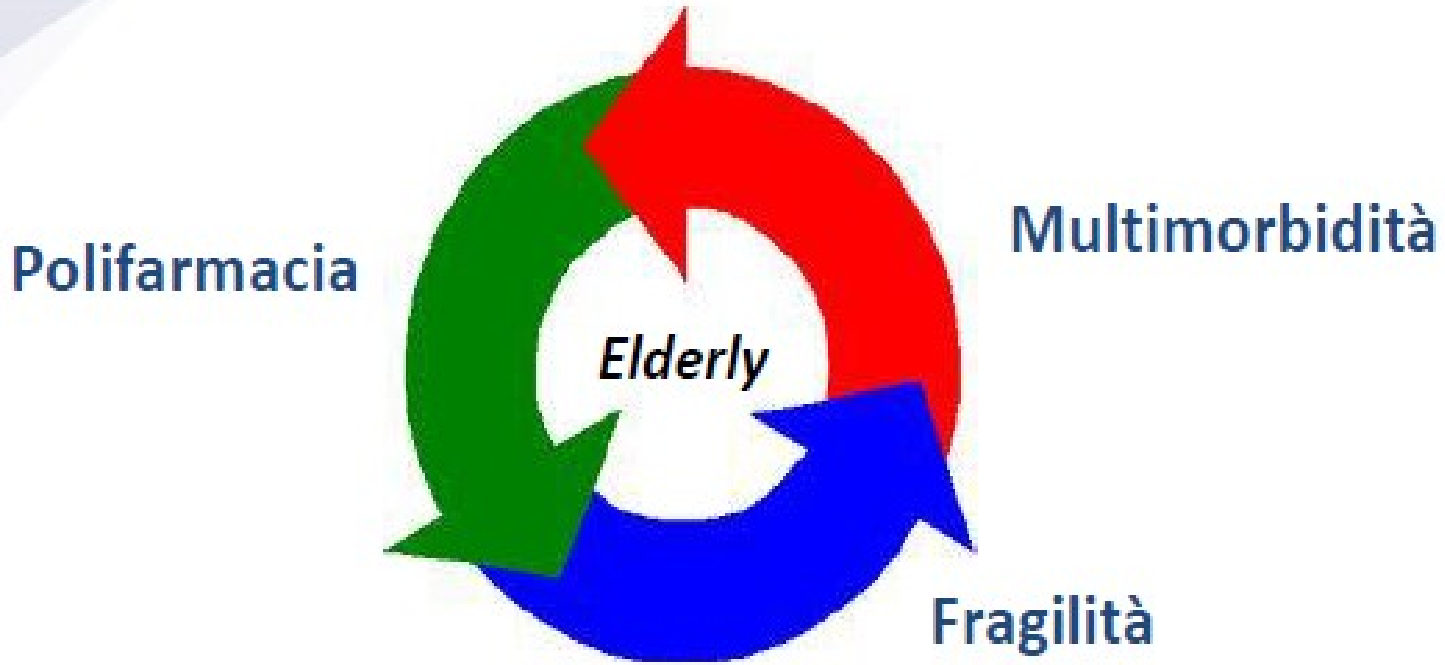
Farmaci antimicotici
Fluconazolo
Itraconazolo
Ketoconazolo
Voriconazolo

Farmaci decongestionanti nasali e antistaminici
Fenilefrina
Fenilpropanolamina
Pseudoefedrina
Terfenadina

Altri farmaci
Alfuzosina
Octreotide
Sibutramina
Tacrolimus
Tamoxifene
Vardenafil

Come identificare il paziente a rischio di tossicità ed interazioni?

- MULTIMORBIDITA': ≥ 2 malattie croniche
- FRAGILITA': > rischio di "outcome" peggiori
- POLIFARMACIA: ≥ 5 farmaci assunti

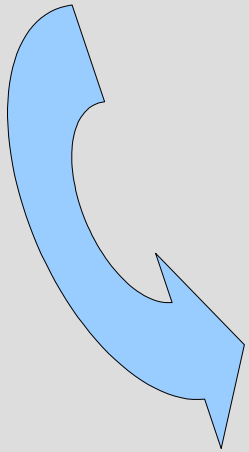


Raccomandazioni EORTC

Minimum dataset for the assessment of global health status and functional status in older cancer patients.

- G8 Questions
- IADL Questions
- Charlson Comorbidity Scale
- Social situation

Pallis et al. Ann Oncol 2011



- Cumulative Illness Rating Scale (CIRS)
- Kaplan–Feinstein Classification (KFC)
- Charlson Comorbidity Index (CCI)
- Index of Co-Existent Disease (ICED)

Comprehensive Geriatric Assessment (CGA)

CGA adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients
Repetto L, Fratino L, Audisio RA, et al. J Clin Oncol 2002; 20: 494-502

Use of Comprehensive Geriatric Assessment in older cancer patients. Recommendations from the Task Force on CGA of the International Society of Geriatric Oncology (SIOG)
Extermann M. et al Critical Rev Oncol Hematol Sept 2005

CRASH Score

- To assess the individual risk of severe toxicity from cht (defined by CTC v. 3.0., as Gr. 4 hemat. or Gr. 3-4 non-hemat. tox) in older pts with diverse health conditions and functional reserve measured by CGA.

  Several variables were analyzed.

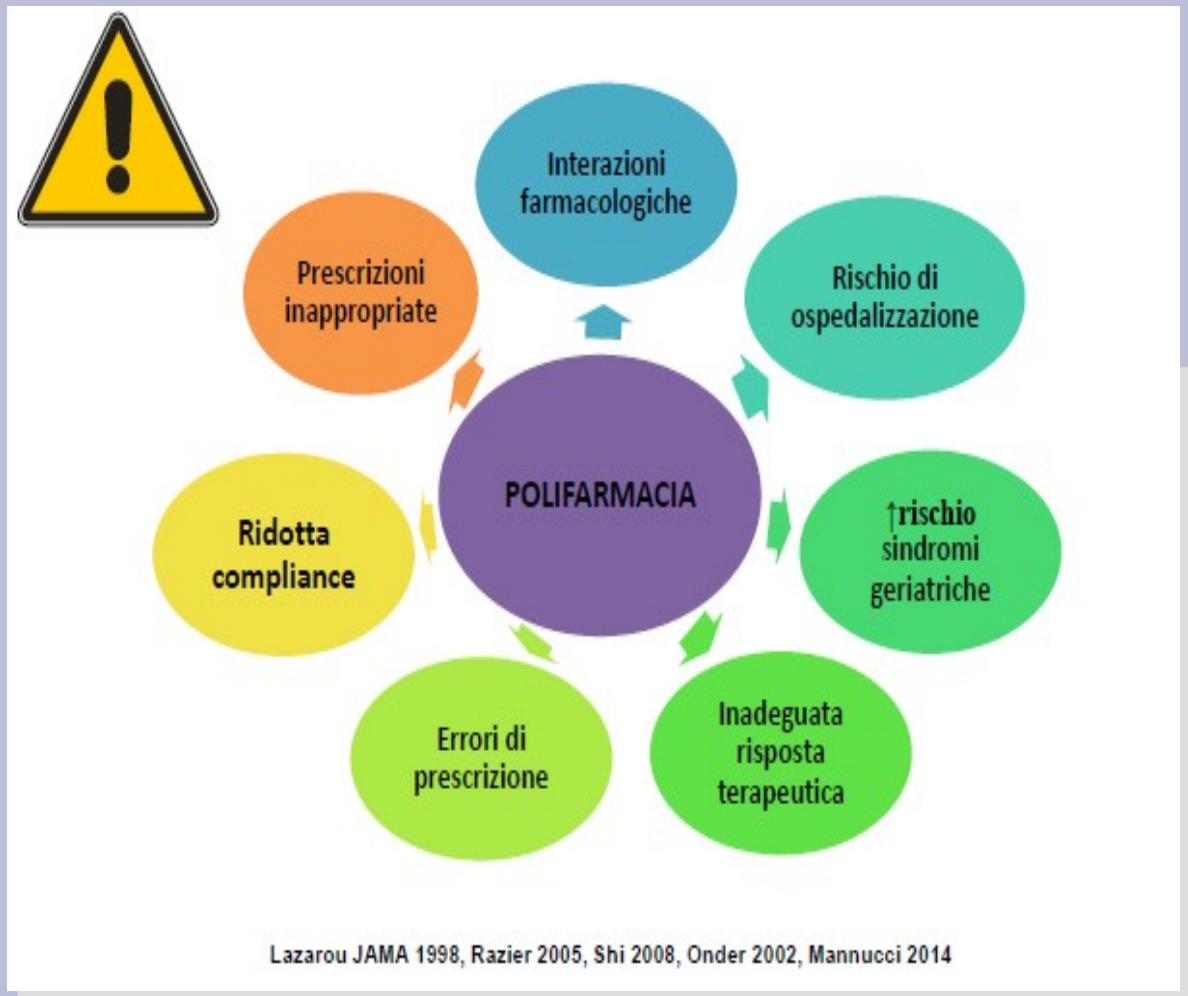
  - age, sex, BMI, diastolic BP (DBP), cancer stage, comorbidity (CIRS-G), polymedication, CBC, liver tests, LDH, creatinine clearance (CrCl), albumin, self-rated health, ECOG PS, IADL, GDS, MMS, MNA, marrow invasion, previous cht, and tumor response

    Cht related toxicity (chemotox) was adjusted using the MAX2 score (*).

- Using this tool
  - LDH, diastolic BP, and chemotox were the best predictive variable for significant differences in the risk of severe haematological toxicity.
  - ECOG-PS, MMS, MNA and chemotox were the best predictive variables for severe non-haematological toxicity.

The CRASH score identifies four categories (0-3, 4-6, 7-9, >9) of older patients with different risk of severe toxicity (from 61% to 100%) (**).

*Extermann EJC 2004 - **Extermann , Cancer 2011



Lazarou JAMA 1998, Razier 2005, Shi 2008, Onder 2002, Mannucci 2014

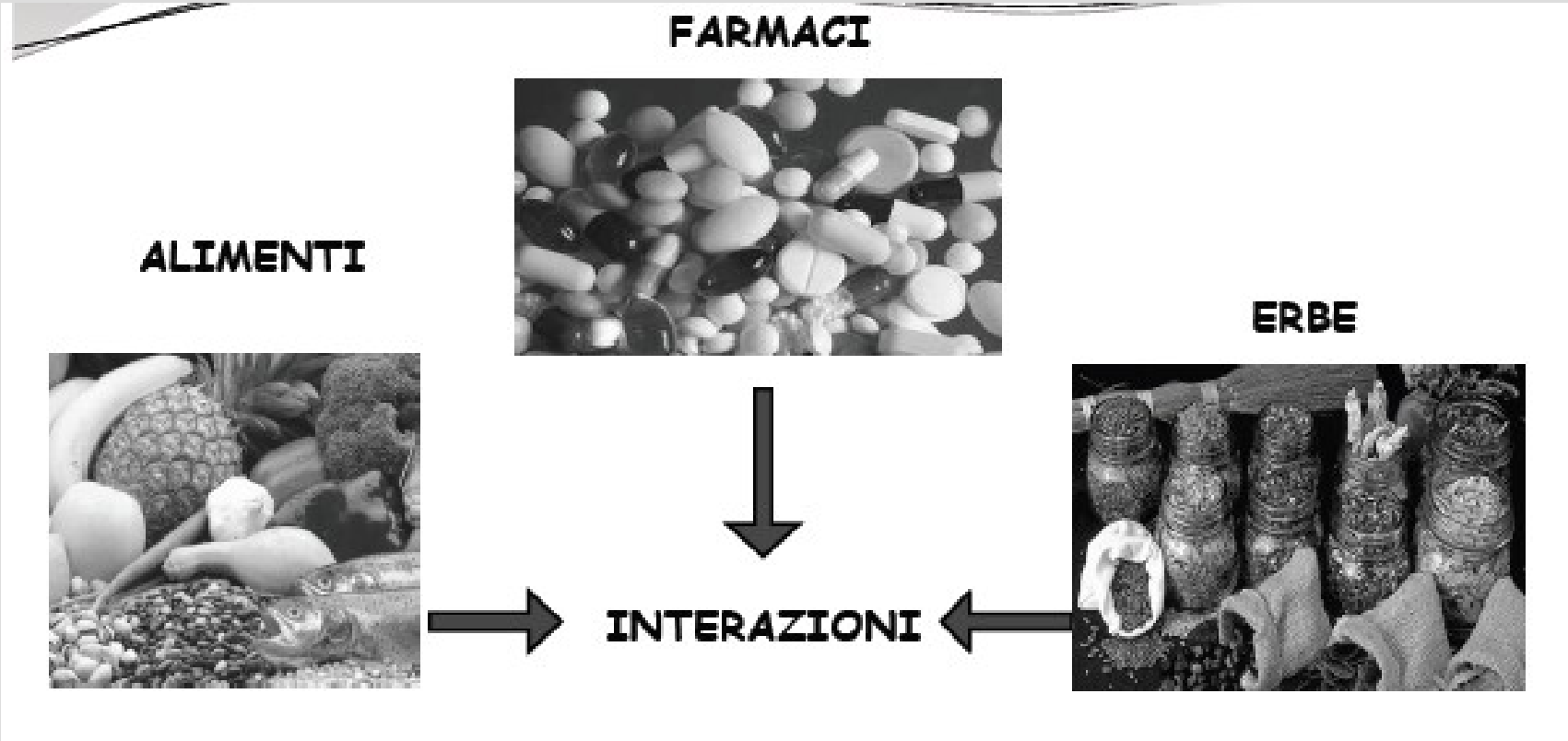
Potential Pitfalls of Disease-Specific Guidelines for Patients with Multiple Conditions

Mary E. Tinetti, M.D., Sidney T. Bogardus, Jr., M.D., and Joseph V. Agostini, M.D.

N ENGL J MED 351;27 WWW.NEJM.ORG DECEMBER 30, 2004

Interazioni tra farmaci si verificano quando la risposta farmacologica o clinica alla somministrazione contemporanea di due o più farmaci o sostanze biologicamente attive è diversa da quella attesa sulla base degli effetti degli stessi somministrati singolarmente.

Le interazioni tra farmaci rappresentano una causa evitabile di risposte imprevedibili e dannose per l'organismo.



Characterizing Drug Interactions

Mechanism

- Pharmacodynamic
  - Receptor inhibition
  - Additive effects
- Pharmacokinetic
  - Altered absorption, distribution, metabolism, or elimination

Interacting agents

Drug - Disease

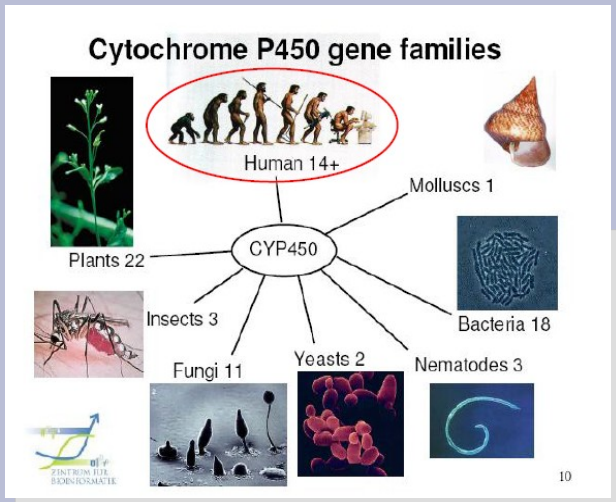
Drug-drug

- Prescription
- Non-prescription
- Illicit, recreational

Food, supplements, herbal products

Clinical Significance

- Major
  - Substantial morbidity and mortality
  - Therapy altering
- Manageable
  - Little or no change in therapy
  - Optimize therapy
- Intentional
  - Additive or synergistic effects
  - Enhanced pharmacokinetics



Human cytochrome P450 family

Of the super-family of all cytochromes, the following families were confirmed in humans:

CYP 1-5, 7, 8, 11, 17, 19, 21, 24, 26, 27, 39, 46, 51

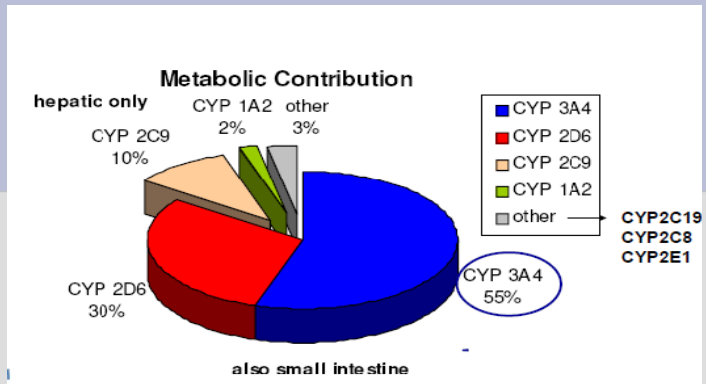
Function:

CYP 1, 2A, 2B, 2C, 2D, 2E, 3 metabolismus of xenobiotica

CYP 2G1, 7, 8B1, 11, 17, 19, 21, 27A1, 46, 51 steroid metabolism

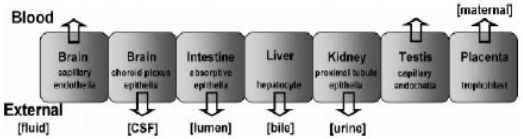
CYP 2J2, 4, 5, 8A1 fatty acid metabolism

CYP 24 (vitamine D), 26 (retinoic acid), 27B1 (vitamine D), ...



P-gp (Glicoproteina –P)

- Fa parte di una ampia super-famiglia di proteine (48 geni, 7 sottofamiglie identificate con lettere A-G) per il trasporto attivo di xenobiotici, ATP-dipendente, note come **ATP-binding cassette (ABC) transporters**
- Compito di questo "network" di trasportatori e' quello di **detossificare e proteggere** l'organismo dagli xenobiotici
- La P-gp e' una proteina di transmembrana (170-kD), nota anche con la sigla ABCB1 o MDR1, in quanto puo' indurre multi-drug-resistance (MDR)
- L'espressione di questa proteina influenza l'ADMET
- Si trova in molti organi: polmoni, intestino, fegato, reni, cervello , testicoli , placenta



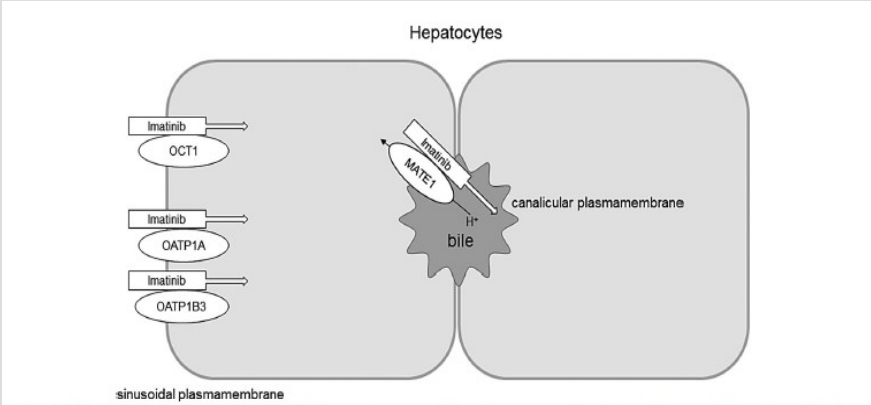


Figure 2. Proposed transport systems for imatinib in human hepatocytes. In the liver, secretion of imatinib into bile canaliculi is performed first by uptake into the hepatocytes through the organic cation transporter 1 (OCT1) and the organic anion-transporting polypeptides 1A and B3 (OATP1A and OATPB3, respectively) expressed in the sinusoidal membrane and then by biliary excretion through the multidrug and toxin extrusion protein 1 (MATE1) expressed in the canalicular hepatocyte membrane.

INDIANA UNIVERSITY

SCHOOL OF MEDICINE
Department of **Medicine**
Clinical Pharmacology

P450 Drug Interactions
Abbreviated "Clinically Relevant" Table
SUBSTRATES

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
clozapine	artemisinin	paclitaxel	**NSAIDs:**	**PPIs:**	**Beta Blockers:**	**Anesthetics:**	**Macrolide antibiotics:**
cyclobenzaprine	bupropion	torsemide	diclofenac	esomeprazole	carvedilol	enflurane	clarithromycin
duloxetine	cyclophosphamide	amodiaquine	ibuprofen	lansoprazole	S-metoprolol	halothane	erythromycin (not 3A5)
fluvoxamine	efavirenz	cerivastatin	naproxen	omeprazole	propafenone	isoflurane	NOT azithromycin
haloperidol	ifosfamide	repaglinide	piroxicam	pantoprazole	timolol	methoxyflurane	telithromycin
imipramine	ketamine					sevoflurane	
mexiletine	meperidine		**Oral Hypoglycemics:**	**Anti-epileptics:**	**Antidepressants:**		
nabumetone	methadone		tolbutamide	diazepam	amitriptyline	**Others:**	**Anti-arrhythmics:**
naproxen	nevirapine		glipizide	phenytoin	clomipramine	acetaminophen→NAPQI	quinidine→3-OH (not 3A5)
olanzapine	propofol		glyburide	phenobarbitone	desipramine	aniline	
riluzole	selegiline				duloxetine	benzene	
tacrine			**Angiotensin II Blockers:**	**Others:**	fluoxetine	chlorzoxazone	**Benzodiazepine**
theophylline			losartan	amitriptyline	imipramine	ethanol	alprazolam
tizanidine			irbesartan	carisoprodol	paroxetine	N,N-dimethyl formamide	diazepam→3OH
triamterene				citalopram			midazolam
zileuton			**Others:**	clomipramine	**Antipsychotics:**	theophylline→8-OH	triazolam
zolmitriptan				clopidogrel	haloperidol		
					risperidone		

Ma tutte le interazioni potenziali sulla base di un meccanismo molecolare accertato o presunto sono rilevanti dal punto di vista clinico?

Assessing the Clinical Relevance of CYP450 Drug Interactions

1. Therapeutic Index and toxic potential of the substrate
2. Alternate pathways of metabolism
3. Role of active metabolites
4. Consequences of metabolic inhibition of metabolites
5. Are multiple P450s inhibited by inhibitor
6. Polymorphism of isoenzyme and patient's metabolizer status
7. Inhibitory potential of metabolites
8. Is inhibition helpful or harmful

Esempio: LLC

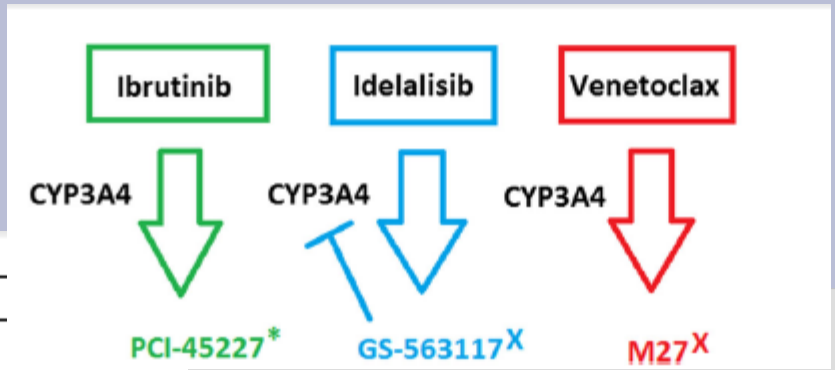
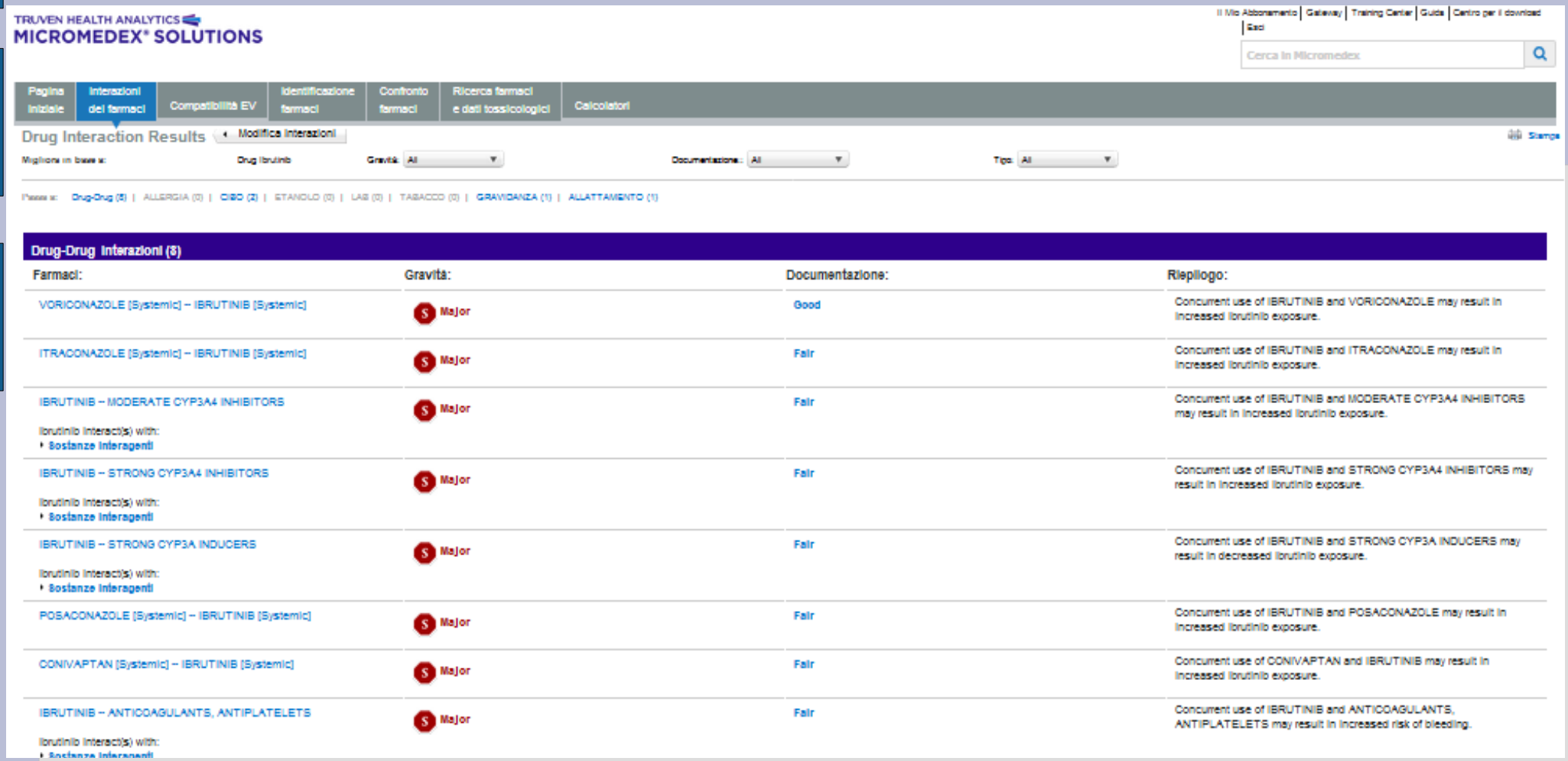


Table 1 Characteristics of ibrutinib, idelalisib, and venetoclax

Characteristic	Ibrutinib	Idelalisib	Venetoclax
Brand name	Imbruvica®	Zydelig®	Venclexta®
Mechanism	Irreversible Btk inhibitor	PI3K-δ inhibitor	Bcl-2 inhibitor
Approved CLL indication	Single-agent therapy for front-line and relapsed/refractory CLL with or without 17p deletion	In combination with rituximab for relapsed CLL in patients for whom rituximab alone would be considered appropriate because of other co-morbidities	Single-agent therapy in patients with 17p deletion who have received at least 1 prior therapy
	In combination with bendamustine and rituximab		
Other indications	Waldenström macroglobulinemia	Follicular lymphoma (monotherapy)	
	Marginal zone lymphoma		
	Relapsed/refractory mantle cell lymphoma		
Standard dose	420 mg daily (560 mg for mantle cell lymphoma)	150 mg twice daily	Dose titration to maximum dose 400 mg daily
Administration	Q24h without regard to meals	Q24h without regard to meals	Q24h with food
Metabolism	Hepatic	Hepatic	Hepatic
Terminal half-life (h)	4–8	8	19
Excretion	Feces	Feces	Feces
Pharmacodynamic parameter	Btk occupancy	Akt concentrations	Lymphocyte count
Common drug interactions	CYP3A4 inhibitors[a] and inducers[b]	CYP3A4 substrates[c]	CYP3A4 inhibitors[d] and inducers[e]
	Anti-platelets or anticoagulants		P-gp inhibitors[d]
	Antacids		
Primary adverse effects	Bleeding	Neutropenia	Tumor lysis syndrome
	Atrial fibrillation Neutropenia	Pyrexia	Neutropenia
	Diarrhea	Nausea	Thrombocytopenia
	Nausea	Headache	Diarrhea
	Dyspepsia	Diarrhea (can be early or late)	Pyrexia
	Arthralgias	Rash	Constipation
	Hepatotoxicity	Transaminitis	Anemia
		Thrombocytopenia	Peripheral edema

M. Waldrom et al. Clin Pharmacokinet (2017) 56:1255–1266

Ibrutinib...



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Drug Interaction Results — Modifica interazioni — Stampa

Migliora in base a: Drug Ibrutinib Gravità: All Documentazione: All Tipo: All

Filtra per: Drug-Drug (8) | ALLERGIA (0) | CIBO (2) | STANCHO (0) | LAB (0) | TABACCO (0) | GRAVIDANZA (1) | ALLATTAMENTO (1)

Drug-Drug Interazioni (8)

Farmaci:	Gravità:	Documentazione:	Riepilogo:
VORICONAZOLE [Systemic] – IBRUTINIB [Systemic]	Major	Good	Concurrent use of IBRUTINIB and VORICONAZOLE may result in increased ibrutinib exposure.
ITRACONAZOLE [Systemic] – IBRUTINIB [Systemic]	Major	Fair	Concurrent use of IBRUTINIB and ITRACONAZOLE may result in increased ibrutinib exposure.
IBRUTINIB – MODERATE CYP3A4 INHIBITORS Ibrutinib interacts with: Sostanze interagenti	Major	Fair	Concurrent use of IBRUTINIB and MODERATE CYP3A4 INHIBITORS may result in increased ibrutinib exposure.
IBRUTINIB – STRONG CYP3A4 INHIBITORS Ibrutinib interacts with: Sostanze interagenti	Major	Fair	Concurrent use of IBRUTINIB and STRONG CYP3A4 INHIBITORS may result in increased ibrutinib exposure.
IBRUTINIB – STRONG CYP3A INDUCERS Ibrutinib interacts with: Sostanze interagenti	Major	Fair	Concurrent use of IBRUTINIB and STRONG CYP3A INDUCERS may result in decreased ibrutinib exposure.
POSACONAZOLE [Systemic] – IBRUTINIB [Systemic]	Major	Fair	Concurrent use of IBRUTINIB and POSACONAZOLE may result in increased ibrutinib exposure.
CONIVAPTAN [Systemic] – IBRUTINIB [Systemic]	Major	Fair	Concurrent use of CONIVAPTAN and IBRUTINIB may result in increased ibrutinib exposure.
IBRUTINIB – ANTICOAGULANTS, ANTIPLATELETS Ibrutinib interacts with: Sostanze interagenti	Major	Fair	Concurrent use of IBRUTINIB and ANTICOAGULANTS, ANTIPLATELETS may result in increased risk of bleeding.

NATURAL MEDICINES
COMPREHENSIVE DATABASE
CONSUMER VERSION

116 interazioni con prodotti erbali

Herbal Supportive Care

La sensazione / opinione comune.....

I prodotti erbali hanno il potenziale di

- Diminuire gli effetti collaterali di diagnostica e terapia oncologica (chirurgia, chemo- e radioterapia)
- Aumentare l'efficacia della terapia (chemosensibilizzazione)
- Migliorare la qualità di vita del paziente oncologico

Pazienti oncologici che combinano prodotti erbali con trattamenti oncologici: 80%.*

Caratteristiche dell'utilizzo:

- Non dichiarato ai medici curanti
- Utilizzo di prodotti di dubbia qualità tecnica
- Utilizzo di dosaggi e modelli di somministrazione non validati

* Xu, W. *Eur. J. Cancer Care* **2006**, *15*, 397-403.

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Herbal Medicines as Adjuvants for Cancer Therapeutics

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[a]Tang Center for Herbal Medicine Research, Pritzker School of Medicine, University of Chicago Chicago, Illinois 60637, U.S.A

Med Oncol (2016) 33:52
DOI 10.1007/s12032-016-0764-6

ORIGINAL PAPER

Risk of interactions between complementary and alternative medicine and medication for comorbidities in patients with melanoma

Carmen Loquai[1] · Dagmar Dechent[2] · Marlene Garzarolli[3] · Martin Kaatz[4] · Katharina C. Kaehler[5] · Peter Kurschat[6] · Frank Meiss[7] · Annette Stein[8] · Dorothee Nashan[7] · Oliver Micke[9] · Ralph Muecke[10] · Karsten Muenstedt[11] · Christoph Stoll[12] · Irene Schmidtmann[13] · Jutta Huebner[14]

Table 3 Biological-based CAM usage of 180 patients with melanoma taking drugs for comorbidities (multiple answers possible)

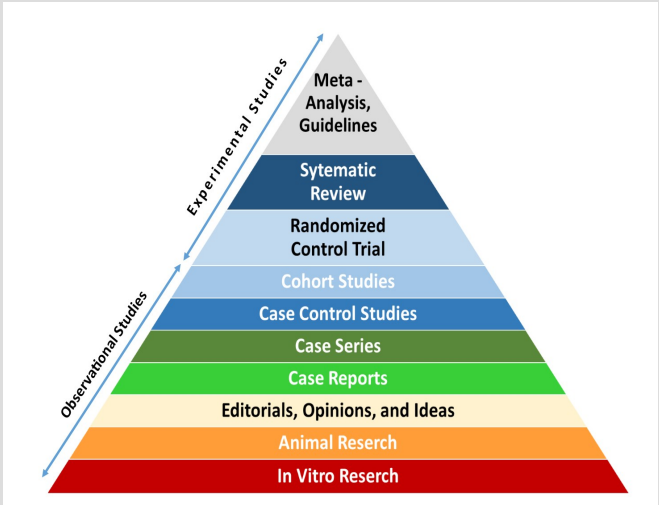
CAM with administration of substances	Number of participants (%)
Vitamins	60 (33.3)
Selenium	42 (24.7)
Other supplements	91 (50.6)
Homeopathy	54 (30.0)
Chinese herbs and teas	35 (19.4)
Enzymes	15 (8.3)
Mistletoe	10 (5.5)
Medical mushrooms	4 (2.2)

December 21 2007 post: I use one and a half or two small squares of cocoa mass, or 100% chocolate (not cocoa powder, mind you). Cocoa mass looks like a regular chocolate bar, and you don't need but a small bit. I melt it over very low heat, but you could use a double boiler, if you prefer. I add a couple of heaping teaspoonfuls of dark organic honey, otherwise it's too bitter to swallow, in my opinion. As soon as these two ingredients have melted (be careful not to burn the mixture, as I have done a couple of times in the past!), I take the pan off the stove and add two grams of quercetin powder and my eight grams of C3 Complex curcumin powder. Stir quickly and eat the mixture even more quickly since it has a tendency to harden. Important note: I put small blobs of it under my tongue, where there are a TON of blood vessels. My idea is to get the dissolved curcumin into the bloodstream without much ado. It would seem that this approach works, which is why I am SO curious to see my next test results.

http://margaret.healthblogs.org/life-with-myeloma/discovery-of-curcumin/my-curcumin-protocol/my-curcumin-cocoa-ma

indena

Come possiamo ricecare informazioni sulle potenziali interazioni e sulla loro rilevanza clinica?



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VOL. 13, NO. 9, 953–972
https://doi.org/10.1080/17425255.2017.1360279

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REVIEW

Curcumin as a clinically-promising anti-cancer agent: pharmacokinetics and drug interactions

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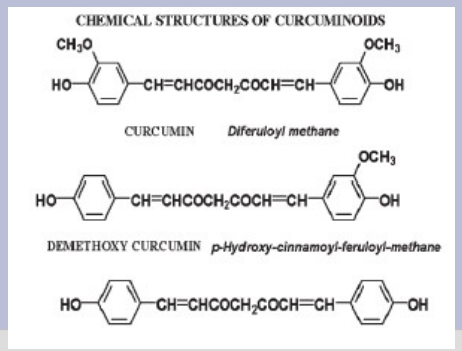
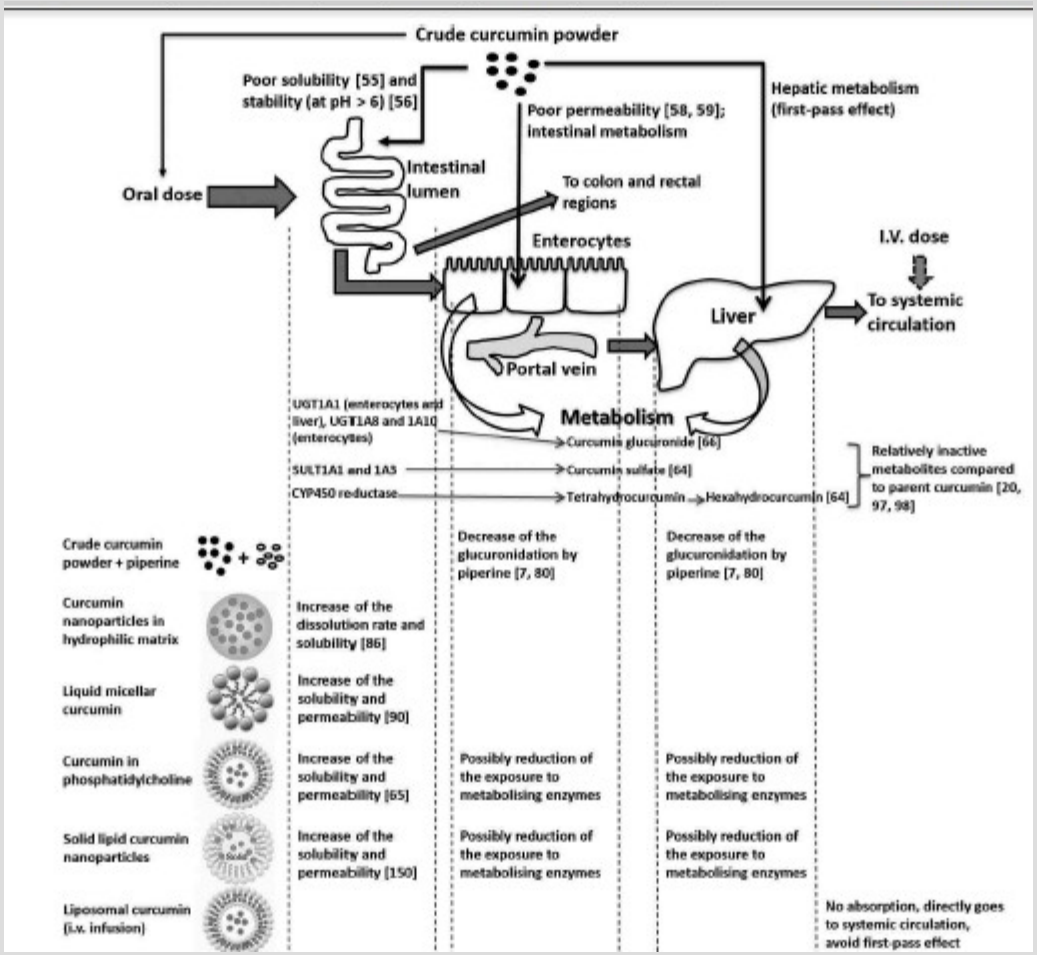
[a]Faculty of Pharmacy, The University of Sydney, Sydney, Australia; [b]Centre for Education and Research on Ageing, Concord Repatriation General Hospital, Concord, Australia





Le interazioni farmacocinetiche della curcumina e dei composti correlati coinvolgono prevalentemente i seguenti sistemi:
- CYP3A4
- i trasportatori ABCB1 e ABCG2.

Il sito di interazione è rappresentato prevalentemente dagli enterociti, vista la scarsa biodisponibilità della curcumina.
Non possono essere escluse interazioni a livello di OATP1B1, MRP1 e MRP2.

Medications changed by the liver (Cytochrome P450 2D6 (CYP2D6) substrates) <<interacts with>> GOLDENSEAL (also known as: Turmeric Root)
Interaction Rating = Moderate Be cautious with this combination.
Talk with your health provider.

Some medications are changed and broken down by the liver. Goldenseal might decrease how quickly the liver breaks down some medications. Taking goldenseal along with some medications that are changed by the liver can increase the effects and side effects of your medication. Before taking goldenseal talk to your healthcare provider if you take any medications that are changed by the liver.

Some medications that are changed by the liver include amitriptyline (Elavil), clozapine (Clozaril), codeine, desipramine (Norpramin), donepezil (Aricept), fentanyl (Duragesic), flecainide (Tambocor), fluoxetine (Prozac), meperidine (Demerol), methadone (Dolophine), metoprolol (Lopressor, Toprol XL), olanzapine (Zyprexa), ondansetron (Zofran), tramadol (Ultram), trazodone (Desyrel), and others.

Medications changed by the liver (Cytochrome P450 3A4 (CYP3A4) substrates) <<interacts with>> GOLDENSEAL (also known as: Turmeric Root)
Interaction Rating = Moderate Be cautious with this combination.
Talk with your health provider.

Some medications are changed and broken down by the liver.

Goldenseal might decrease how quickly the liver breaks down some medications. Taking goldenseal along with some medications that are broken down by the liver can increase the effects and side effects of some medications. Before taking goldenseal, talk to your healthcare provider if you are taking any medications that are changed by the liver.

Some medications changed by the liver include lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and many others.

Digoxin (Lanoxin) <<interacts with>> GOLDENSEAL (also known as: Turmeric Root)
Interaction Rating = Moderate Be cautious with this combination.
Talk with your health provider.

Taking goldenseal with digoxin (Lanoxin) might cause a very slight increase in digoxin (Lanoxin) levels in the body. But this does not seem to be an important interaction.

Medications moved by pumps in cells (P-Glycoprotein Substrates) <<interacts with>> GOLDENSEAL (also known as: Turmeric Root)
Interaction Rating = Moderate Be cautious with this combination.
Talk with your health provider.

Some medications are moved by pumps in cells. Goldenseal might make these pumps less active and increase how much of some medications get absorbed by the body. This might increase the amount of some medications in the body, which could lead to more side effects. But there is not enough information to know if this is a big concern.

Some medications that are moved by these pumps include etoposide, paclitaxel, vinblastine, vincristine, vindesine, ketoconazole, itraconazole, amprenavir, indinavir, nelfinavir, saquinavir, cimetidine, ranitidine, diltiazem, verapamil, corticosteroids, erythromycin, cisapride (Propulsid), fexofenadine (Allegra),

Clinical Evidence of Herbal Drugs As Perpetrators of Pharmacokinetic Drug Interactions

Robert Hermann [1], Oliver von Richter [2]

[1] Clinical Research Appliance, Radolfzell, Germany
[2] Merck Serono, Darmstadt, Germany

present review, were identified. The clinical evidence was found to be most robust and informative for *Gingko biloba* (GB; 21 studies) and milk thistle/silymarin (MT; 13), and appears still limited for ginseng (9), goldenseal/berberine (GS; 8), garlic (8), and *Echinacea* (7). Collectively, the available evidence indicates that, at commonly recommended doses, none of these herbs act as potent or moderate inhibitors or inducers of cytochrome P450 (CYP) enzymes or P-glycoprotein (ABCB1). Weak effects in terms of either induction or inhibition were found for GB (presystemic/hepatic CYP3A4 induction/inhibition, CYP2C19 induction at high doses), milk thistle/silymarin (CYP2C9 inhibition), GS/berberine (CYP3A4 and CYP2D6 inhibition), *Echinacea* (presystemic/hepatic CYP3A4 inhibition/induction, CYP1A2 and CYP2C9 inhibition at high doses). Information was found not always complete for the major drug metabolizing CYP enzymes in the less well-studied herbs and is largely limited to P-glycoprotein (ABCB1) when effects on drug transporters have been investigated.

Relevance of *in vitro* and clinical data for predicting CYP3A4-mediated herb–drug interactions in cancer patients

Andrew K.L. Goey[a,e,f], Kim D. Mooiman[a,e,g], Jos H. Beijnen[a,c,h], Jan H.M. Schellens[a,d,i], Irma Meijerman[b,*]

Table 3a
Effect of garlic on the activity of CYP3A4 *in vitro*.

Models	CAM/component	Garlic product	Assay	Results	Ref.
Supersomes™	0–98 μM allicin	LKT Laboratories, St. Paul, USA	Fluorescence assay (BFC)	↓ CYP3A4 activity IC_{50} = 43.73 μM	65
			Fluorescence assay (BzRes)	↓ CYP3A4 activity IC_{50} = 60.10 μM	
	25 mg/mL garlic extracts	Local commercial outlets, Ottawa, USA	Fluorescence assay (BzRes)	17.4–95.8% ↓ CYP3A4 activity	64
	0–5 ng/mL garlic	Local pharmacy, Bremen, Germany	HPCL-UV (testosterone)	↔ CYP3A4 activity	67
Fa2N-4 cells	0–200 μg/mL garlic extract	Nature's Way, Springville, USA	RT-PCR LC-MS (midazolam)	↔ mRNA and CYP3A4 activity	68
Human hepatocytes	0.1 μg/mL garlic	Local commercial outlets, Ottawa, USA	Northern blotting	2 times ↑ mRNA	69
HepG2 cells	0.1 μg/mL garlic	Local commercial outlets, Ottawa, USA	Reporter gene assay	No fold induction of CYP3A4	69

Abbreviations: BFC = 7-benzyloxy-4-trifluoromethylcoumarin; BzRes = 7-benzyloxyresorufin; HPLC-UV = high-performance liquid chromatography with ultraviolet detection; LC-MS = liquid chromatography mass spectrometry; RT-PCR = real-time polymerase chain reaction; IC_{50} = half maximal inhibitory concentration. ↔ = unchanged, ↓ = decrease.

Table 3b
Effect of garlic on the pharmacokinetics of selected substrate drugs in healthy volunteers and patients.

Subjects	Dose garlic	Garlic product	Substrate	Results	Ref.
Healthy volunteers (n = 12)	500 mg garlic oil, thrice daily, 28 days	Wild Oats Markets, Inc., Boulder, USA	MDZ (P.O.)	No sign. effect on 1-OH MDZ/MDZ serum ratio	31
Healthy volunteers (n = 12)	500 mg garlic oil, thrice daily, 28 days	Vitamer, Lake Forest, USA	MDZ (P.O.)	No sign. effect on 1-OH MDZ/MDZ serum ratio	30
Breast cancer patients (n = 10)	600 mg (3600 μg allicin), twice daily, 12 days	GarliPure, Maximum Allicin Formula, Natrol, Chatsworth, USA	Docetaxel (IV)	No sign. effect on AUC_{0-24} docetaxel	71

Abbreviations: AUC_{0-24} = area under the plasma concentration–time curve from 0–24 h; no sign. = not statistically significant; 1-OH MDZ = 1-hydroxymidazolam; MDZ = midazolam; P.O. = oral administration; IV = intravenous administration.

Table 2a
Effect of milk thistle on the activity of CYP3A4 in vitro.

Models	CAM/component	Milk thistle product	Assay	Results	Ref.
HLM	MT extract (normalized to 10 μM silibinin)	Indena USA Inc., Seattle, USA	HPLC-UV (midazolam and testosterone)	43% ↓ CYP3A4 activity	51
	100 μM silymarin	Madaus GmbH, Cologne, Germany	LC-MS (testosterone)	>90% ↓ CYP3A4 activity	52
	0–100 μM silibinin	Ivax-CR, Opava, Czech Republic	HPLC-UV (nifedipine)	↓ CYP3A4 activity IC_{50} = 27 & 60 μM	53
	0–300 μM silibinin	Purified and provided by Dept. of Chemistry, Madaus, Germany	HPLC-UV (nifedipine)	↓ CYP3A4 activity IC_{50} = 29 & 46 μM	55
	0–400 μM silibinin	Ivax-CR, Opava, Czech Republic	HPLC-UV (testosterone)	↓ CYP3A4 activity IC_{50} = 49.8 μM	54
Human hepatocytes	100 μM silymarin	Sigma, St. Louis, USA	HPLC-UV (testosterone)	50% ↓ CYP3A4 activity	56
	0–100 μM silibinin	Purified and provided by Galena Opava a.s., Czech Republic	Northern blotting	↔ mRNA, protein	58
E. coli MV1304 cells	0–250 μM silibinin	Sigma–Aldrich, St. Louis, USA	HPLC-UV (testosterone)	↓ CYP3A4 activity K_i = 132 μM	57
Baculosomes	0–50 μM silibinin	Sigma Chemical Co., St. Louis, USA	Fluorescence assay(Vivid red)	↔ CYP3A4 activity	37
	0–50 μM silibinin	Sigma Chemical Co., St. Louis, USA	HPLC-UV (cortisol)	↔ CYP3A4 activity	
Caco-2 cells	0–75 μg/mL MT extracts	Local retail outlets, Ottawa, USA	RT-PCR and Western blotting	↓ mRNA, protein	39
	0–10 μM silibinin	Sigma–Aldrich, St. Louis, USA	RT-PCR and Western blotting	↓ mRNA, ↑ protein	

Abbreviations: HLM = human liver microsomes; HPLC-UV = high-performance liquid chromatography with ultraviolet detection; LC-MS = liquid chromatography mass spectrometry; MT = milk thistle; RT-PCR = real-time polymerase chain reaction; IC_{50} = half maximal inhibitory concentration; K_i = in vitro inhibition constant. ↔ = unchanged, ↓ = decrease.

Table 2b
Effect of milk thistle on the pharmacokinetics of selected substrate drugs in healthy volunteers and patients.

Subjects	Dose milk thistle	Milk thistle product	Substrate	Results	Ref.
Healthy volunteers (n = 12)	175 mg (80% silymarin), twice daily, 28 days	Wild Oats Markets, Inc, Boulder, USA	MDZ (P.O.)	No sign. effect on 1-OH MDZ/MDZ serum ratio	60
Healthy volunteers (n = 19)	300 mg (80% silymarin), thrice daily, 14 days	Enzymatic Therapy, Inc, Green Bay, USA	MDZ (P.O.)	No sign. effect on $AUC_{0-\infty}$ MDZ, and 1-OH MDZ/MDZ serum ratio	61
Cancer patients (n = 6)	200 mg (80% silymarin), thrice daily, 4 and 12 days	GNC, Pittsburgh, USA	Irinotecan (IV)	No sign. effect on AUC irinotecan, SN-38, SN-38G, APC.	47

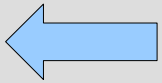
Abbreviations: $AUC_{0-\infty}$ = area under the serum concentration–time curve from time zero extrapolated to infinity; no sign. = not statistically significant; 1-OH MDZ = 1-

Table 1b
Effect of SJW on the pharmacokinetics of selected substrate drugs in healthy volunteers and patients.

Subjects	Dose SJW	SJW Product	Substrate	Results	Ref.
Healthy volunteers (n = 12)	300 mg (0.3% hypericin), thrice daily, 14 days	Sundown Herbals, Boca Raton, USA	MDZ (P.O., IV)	52% ↓ $AUC_{0-\infty}$ oral MDZ, 21% ↓ $AUC_{0-\infty}$ IV MDZ	41
	300 mg (0.3% hypericin), thrice daily, 8 weeks	Rexall-Sundown Pharmaceuticals, Boca Raton, USA	MDZ (P.O., IV)	53% ↑ CL oral MDZ, 3% ↑ CL IV	42
	300 mg, thrice daily, 14 days	TruNature, Leiner Health Products, Carson, USA	MDZ (P.O.)	33% ↑ CL oral MDZ, baseline CL MDZ restored 7 days after completion	85
	300 mg (0.3% hypericin), thrice daily, 28 days	Vitamer, Lake Forest, USA	MDZ (P.O.)	141% ↑ 1-OH MDZ / MDZ serum ratio	30
	300 mg (0.3% hypericin), thrice daily, 28 days	Wild Oats Markets, Inc, Boulder, USA	MDZ (P.O.)	98% ↑ 1-OH MDZ / MDZ serum ratio	31
Healthy volunteers (n = 20)	500 mg, twice daily, 14 days	Kneipp Werke, Würzburg, Germany	MDZ (P.O.)	15% ↓ $AUC_{0-\infty}$ oral MDZ	46
Healthy volunteers (n = 21)	300 mg (0.3% hypericin), thrice daily, 12 days	Jarsin 300 dragée, Li 160, Lichtwer Pharma AG, Berlin, Germany	MDZ (P.O., IV)	168% ↑ CL oral MDZ, 44% ↑ CL IV MDZ	43
Healthy volunteers (n = 30)	300 mg, thrice daily, 10 days	UK	MDZ (P.O., IV)	190% ↑ CL oral MDZ, 56% ↑ CL IV MDZ	44
Healthy volunteers (n = 42)	300–900 mg, twice/thrice daily, 14 days	1: Jarsin 300 dragée, Li 160, Lichtwer Pharma AG, Berlin, Germany 2A: Type A, Kneipp Werke, Würzburg, Germany 2B: Kneipp Johanniskraut Dragees H, Kneipp Werke, Würzburg, Germany	MDZ (P.O.)	↓ AUC oral MDZ (sign. correlation with hyperforin content)	45
Cancer patients (n = 5)	300 mg, thrice daily, 18 days	Bio Nutrition Health Products, Den Bosch, The Netherlands	Irinotecan (IV)	42% ↓ AUC SN-38, ↓ myelosuppression	10
Healthy volunteers (n = 12)	300 mg, thrice daily, 14 days	Kira, Li 160, Lichtwer Pharma AG, Berlin, Germany	Imatinib (P.O.)	30% ↓ $AUC_{0-\infty}$	12
Healthy volunteers (n = 10)	300 mg, thrice daily, 14 days	HBC Inc., Los Angeles, USA	Imatinib (P.O.)	32% ↓ $AUC_{0-\infty}$	11

Abbreviations: P.O. = oral administration; IV = intravenous administration; 1-OH MDZ = 1-hydroxymidazolam; MDZ = midazolam; CL = total plasma clearance; UK = unknown; $AUC_{0-\infty}$ = area under the plasma concentration–tim curve from time zero to infinity; ↓ = decrease and ↑ = increase.

This review summarizes that *in vitro* data are used to discover effects of CAM on CYP3A4 and for certain CAM, such as SJW, these effects can be extrapolated to clinical studies. Occassionally, significant effects on CYP3A4 *in vitro* do not predict significant interactions in clinical trials. These discrepancies can be largely attributed to differences between *in vitro* test systems and the physiological environment. To improve extrapolation from *in vitro* to the clinic, *in vitro* conditions should closely mimic physiological conditions, as accurate prediction of clinical pharmacokinetic interactions is complicated by several factors (e.g. poor pharmaceutical availability, solubility and bioavailability of CAM). Therefore, clinical studies are required for confirmation and assessment of the clinical relevance of CAM–drug interactions obtained *in vitro*. In clinical trials midazolam has been shown to be a useful probe drug to correctly predict the presence or absence of clinical CYP3A4-based interactions between CAM and anticancer drugs.



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Evaluation of drug–drug interactions for oncology therapies: *in vitro–in vivo* extrapolation model-based risk assessment

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Keywords
anti-cancer therapy, CYP3A, CYP induction, CYP inhibition, drug interactions, pharmacokinetics

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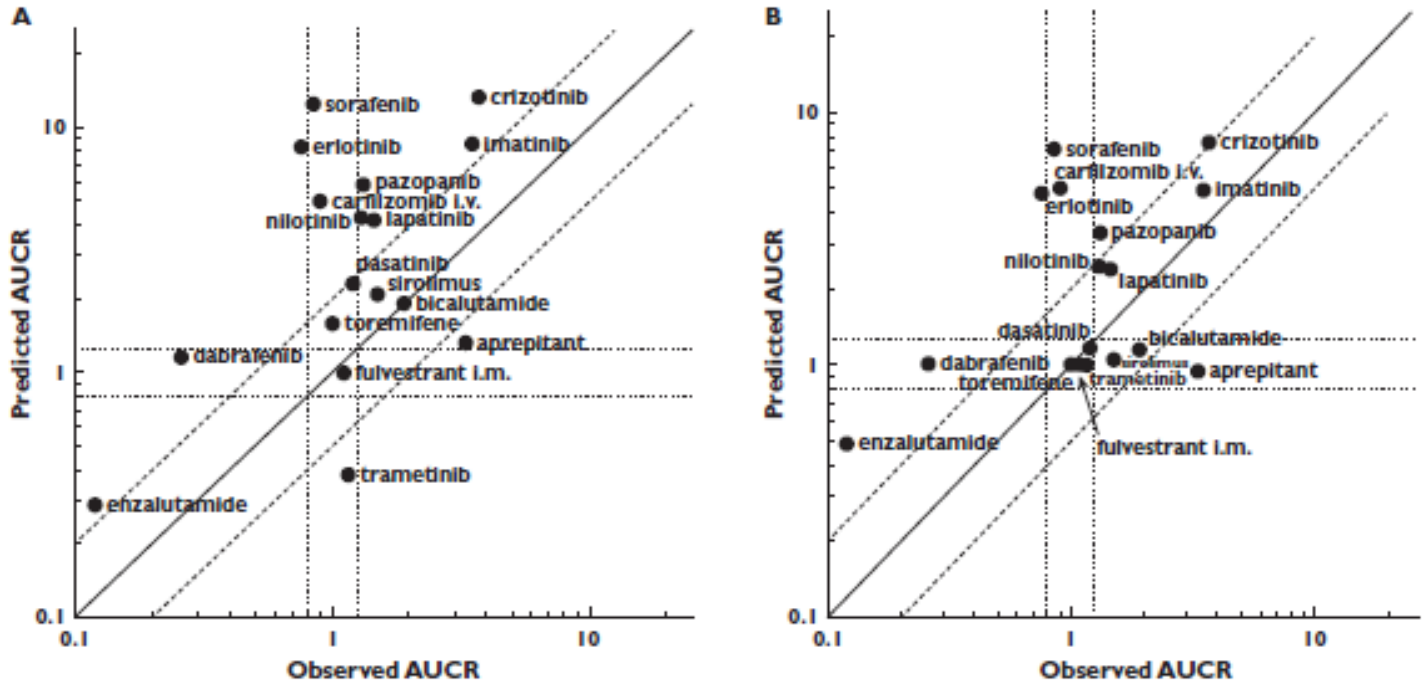

Figure 1

Observed *vs.* predicted AUCR for oncology drugs as perpetrators of CYP3A DDI using the mechanistic static model for liver and intestine (A) and liver only (B). AUCR threshold of 0.8 and 1.25 shown as dotted lines as well as line of unity and 2-fold error lines

Complichiamo ancora un po' il quadro…..

Gut microbiota modulation of chemotherapy efficacy and toxicity

James L. Alexander[1,3], Ian D. Wilson[3], Julian Teare[1], Julian R. Marchesi[1–3], Jeremy K. Nicholson[3] and James M. Kinross[1,3]

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Bioactivity Enhancement of Herbal Supplements by Intestinal Microbiota Focusing on the Ginsenosides

Huai-You Wang[1], **Lian-Wen Qi**[1,2,*], **Chong-Zhi Wang**[2], and **Ping Li**[1,*]

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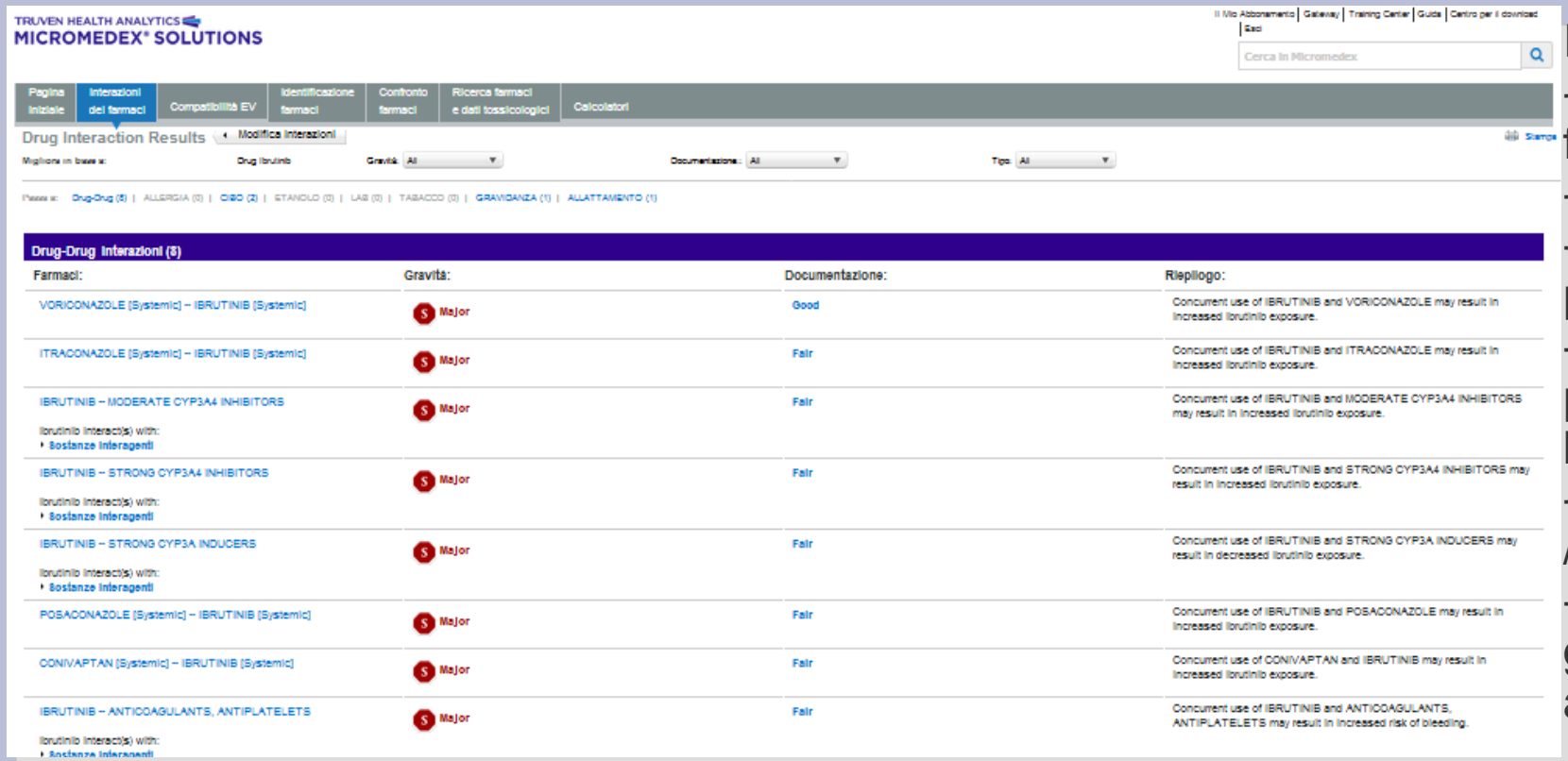
I database dedicati alle interazioni

Micromedex

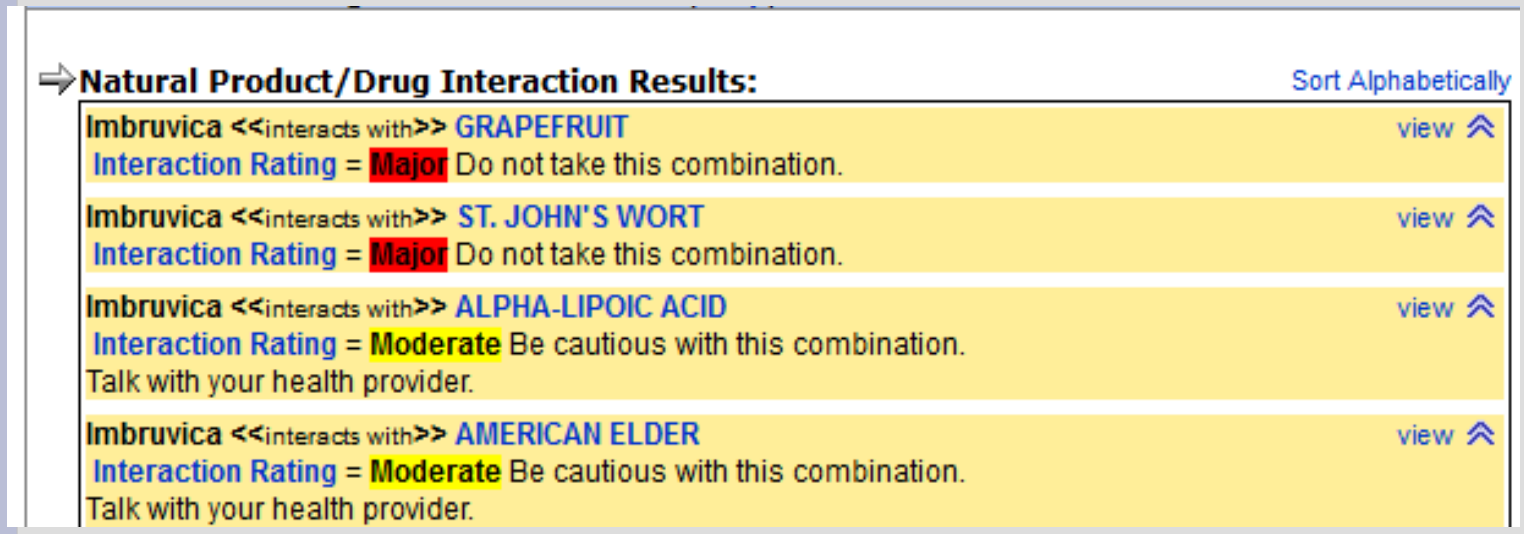


Interazioni:
- farmaco / farmaco
- farmaco / cibo
- farmaco / prodotti naturali
- farmaco / parametri di laboratorio
- farmaco /etanolo
- farmaco / gravidanza e allattamento

- Le informazioni relative alle interazioni con i prodotti naturali sono molto limitate
- Utile la classificazione di gravità dell'interazione
- Utile la presenza della documentazione bibliografica a supporto dell'interazione e la valutazione della sua qualità

I database dedicati alle interazioni

Natural Medecines Comprehensive Database



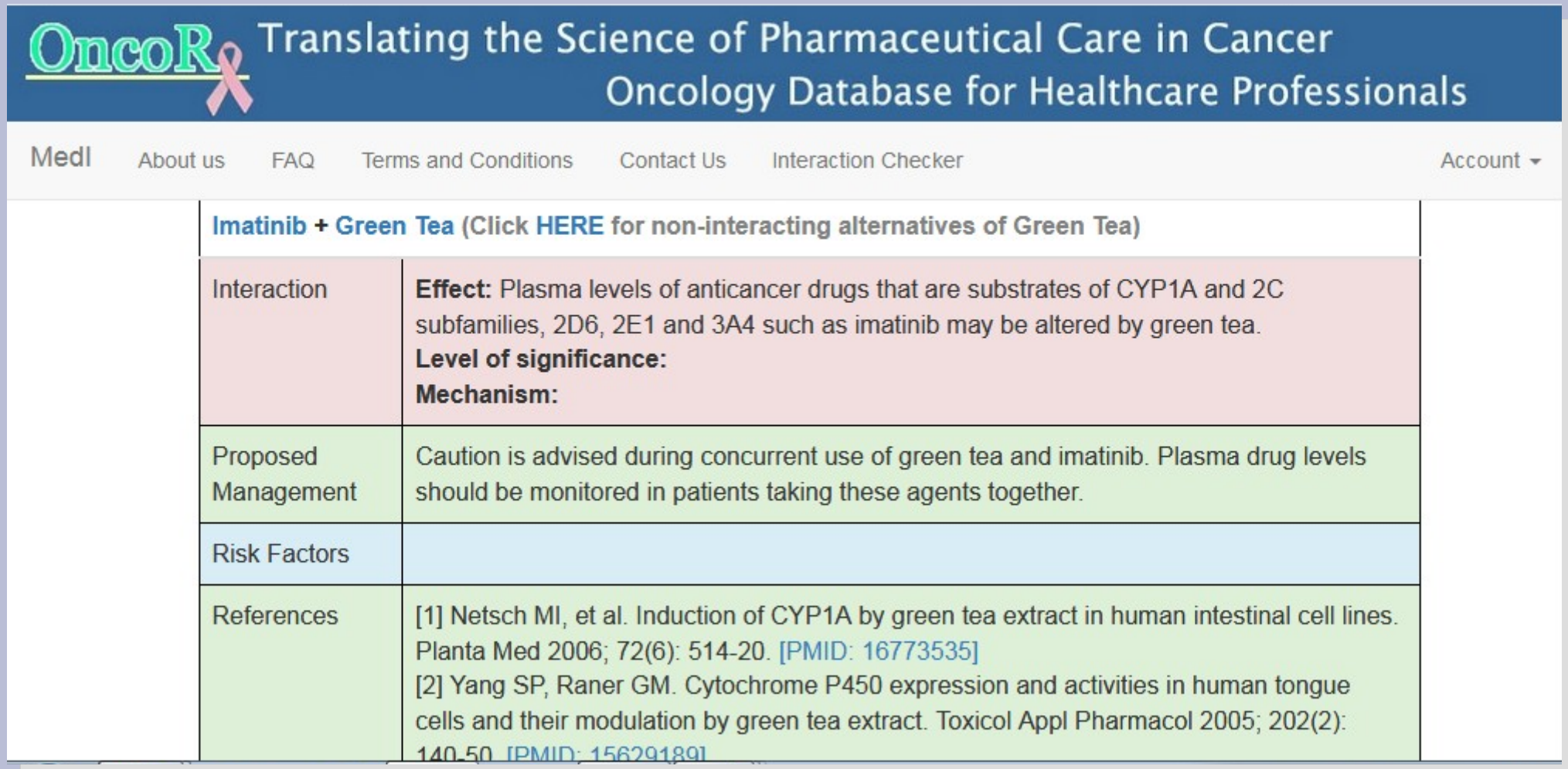
- Possibili molteplici possibilità di ricerca singola e multipla
- Contiene schede monografiche e approfondimenti su specifiche sostanze / prodotti / tipologie di interazione

- Sono tutte interazioni potenziali basate sul sistema CYP450, ma in gran parte "teoriche".
- Il livello di rilevanza è anch'esso teorico, perché desunto dalla relativa capacità dei componenti del prodotto di agire come induttori / inibitori del CYP450
- Sono riportate pochissime informazioni su modalità di interazione che coinvolgono sistemi diversi dal CYP450
- Sono riportate informazioni su interazioni non legate a meccanismi molecolari specifici

Database a pagamento...di libera consultazione solo la "Consumer Version"

I database dedicati alle interazioni

Natural Medecines Comprehensive Database



OncoR Translating the Science of Pharmaceutical Care in Cancer
Oncology Database for Healthcare Professionals

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Imatinib + Green Tea (Click HERE for non-interacting alternatives of Green Tea)

Interaction	**Effect:** Plasma levels of anticancer drugs that are substrates of CYP1A and 2C subfamilies, 2D6, 2E1 and 3A4 such as imatinib may be altered by green tea. **Level of significance:** **Mechanism:**
Proposed Management	Caution is advised during concurrent use of green tea and imatinib. Plasma drug levels should be monitored in patients taking these agents together.
Risk Factors	
References	[1] Netsch MI, et al. Induction of CYP1A by green tea extract in human intestinal cell lines. Planta Med 2006; 72(6): 514-20. [PMID: 16773535] [2] Yang SP, Raner GM. Cytochrome P450 expression and activities in human tongue cells and their modulation by green tea extract. Toxicol Appl Pharmacol 2005; 202(2): 140-50. [PMID: 15629189]

I database dedicati alle interazioni

Transformer

http://bioinformatics.charite.de/transformer/

TRANSFORMER

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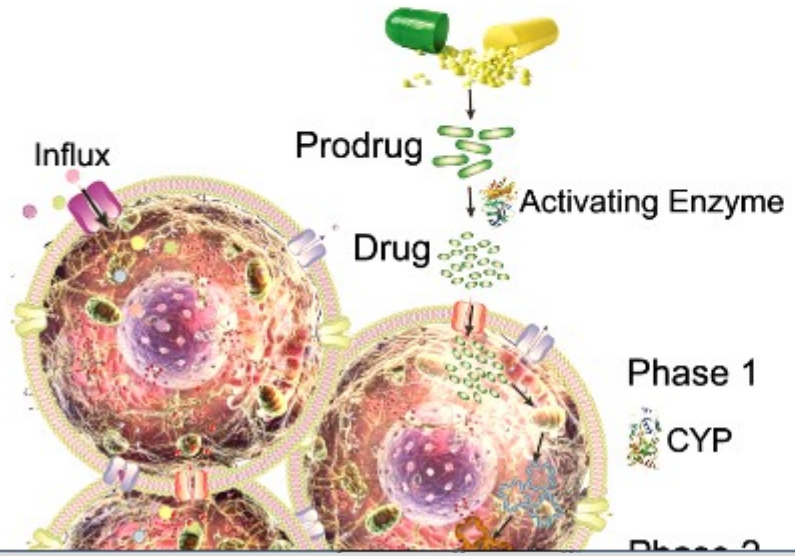
Transformer - Metabolism of Xenobiotics Database

Drug Transformation



Transformer

Welcome to the open access database Transformer! It provides comprehensive information on the transformation and transport of xenobiotics in the human body. It contains the interactions of phase I and II enzymes and drug transporters with drugs, prodrugs, alimentary and Traditional Chinese Medicine compounds.
A particular highlight is the ability to detect mutual effects of several drugs. To this end, the cocktail tool displays interactions of drugs on the basis of their effect on the enzymes and transporters. Suggestions of alternative medications with appropriate indication, based on ATC-code, are provided. If you are using Transformer, please give us credit by linking to Transformer and citing the

Accepted: 19 July 2017
DOI: 10.1111/ecc.12752

ORIGINAL ARTICLE

WILEY European Journal of Cancer Car

Development of a rapid risk evaluation tool for herbs/drugs interactions in cancer patients: a multicentric experience in south of France

B. Pourroy[1] | C. Letellier[2] | A. Helvig[3] | B. Chanet[4] | F. De Crozals[4] | C. Alessandra

TABLE 5 HDI risk analysis tool

	SJW *Hypericum perforatum*	Milk Thistle *Silybum marianum*	Garlic *Allium sativum*	Ginkgo *Ginkgo Biloba*	Purple Echinacea *Echinacea purpurea*	Ginseng *Panax ginseng*	Curcuma *curcuma longa*	Licorice *Glycirrhiza glabra*	Black Chokeberry *Aronia melanocarpa*	Rhubarb *Rheum sp.*	Green tea *Camellia sinensis*
Abiraterone	3	2	2	2	2	2	0	0	0	0	0
Acide 5-aminolevulinique	0	0	0	0	0	0	0	0	0	0	0
Aflibercept	1	1	3	3	1	3	0	3	0	0	0
Alitretinoïne	3	2	2	2	2	2	0	0	0	0	0
Altretamine	0	0	0	0	2	0	0	0	0	0	0
Amsacrine	0	0	0	0	2	0	0	0	0	0	0
Anagrelide	0	0	0	0	2	0	0	0	0	0	0
Anastrozole	0	0	0	1	0	0	0	0	0	0	0
Arsenic trioxyde	0	0	0	0	2	0	0	0	0	0	0
Asparaginase	1	1	1	1	1	1	0	0	0	0	0
Axitinib	3	2	2	3	2	3	0	3	0	0	0
Azacitidine	0	0	0	0	2	0	0	0	0	0	0
Bendamustine	0	0	0	0	2	0	0	0	0	0	0
Bevacizumab	1	1	3	3	1	3	0	3	0	0	0
Bexarotène	3	2	2	2	2	0	0	0	0	0	0
Bicalutamide	3	2	2	2	0	2	0	0	0	0	0
Bleomycine	0	0	0	0	2	0	0	0	0	0	0
Bortezomib	3	2	2	2	2	2	0	0	0	0	0
Bosutinib	3	2	3	2	2	2	3	3	0	0	0
Brentuximab vedotin	3	2	3	2	2	2	3	0	0	0	0
Busereline	0	0	3	0	0	0	0	0	0	0	0
Busulfan	0	0	0	0	2	0	0	0	0	0	0
Cabazitaxel	3	2	3	2	2	2	3	0	0	0	0

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Herbs and Other Dietary Supplements in Cancer Care

Patients and caregivers often have questions about taking vitamins, herbal and dietary supplements, and the safety of these products. This course prepares clinicians to address risk and prevent herb-drug interactions.

Credit: 6 NCCAOM PDA points

General Approach to Managing Drug Interactions

- Each contact with the patient includes a review of all medications - prescribed and OTC.
- Information on medications prescribed by any and all health-care providers is reviewed
- Specifically query for problematic food and nutriceutical products
- Keep a high "Index of Suspicion" for all toxic events and therapeutic failures
- When possible, use agents which are the *least* problematic
- Sometimes, timing of doses may minimize interactions, especially with food
- Proactively instruct patients about avoiding interactions
- Usually, management of interactions requires minimal alterations in therapeutic plan