

Master Virtuale A.R.E.O

Terapie oncologiche continuative orali: il problema della compliance e la gestione degli effetti collaterali. Condivisione con il MMG della gestione della terapia

Valentina Guarneri MD, PhD

Department of Oncology, Hematology and Respiratory Diseases, Modena University Hospital

Oral cancer therapy

- In cancer therapy, patient-administered oral medications have played a relatively minor role versus iv cytotoxic therapy
- The past decade has seen an accelerating expansion of the development of oral anticancer drugs
- This trend is expected to continue, and more than one quarter of the 400 antineoplastic agents currently in the pipeline are planned as oral drugs

Oral cancer therapy in 2009


- **Cytotoxic**

- Capecitabine
- Vinorelbine
- Methotrexate
- Idarubicin
- Cyclophosphamide
- Etoposide
- Temozolamide
- Tegafur
- Chlorambucil
-

- **Targeted agents**

- SERMS
- AI
- TKIs (lapatinib, erlotinib, sorafenib, sunitinib, imatinib..)

- **Supportive medications**



General Considerations- Adherence in non-oncologic settings

- Treatment adherence is one of the most complex problems in medical management.
- Adherence is better in acute than chronic conditions
- Rates of persistence generally fall off abruptly at ~6 mos
- Physicians are poor at identifying/predicting nonadherence
- Elderly are particularly at risk because of the amount of medication they receive.



Adherence - Compliance

- The potential problem of nonadherence has received greater recognition
- The ISPOR* recently defined adherence synonymous with compliance: “the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency.”
- Persistence: duration of time from the initiation to the discontinuation

*International Society for Pharmacoeconomics and Outcome Research



Adherence - Compliance

- A patient is optimally adherent if:
 - No doses are missed
 - No extra doses are taken
 - No doses are taken in the wrong quantity or at the wrong time
- A patient is optimally persistent when taking a medication as long as it is prescribed
- Overadherence may also be problematic because safety is impaired



Adequate adherence

- There is no consensus regarding a definition of “adequate adherence”
- Investigators use ranges between 80-95%, although there are limited data to support this threshold
- The following classification has been proposed to account for a range of adherent behaviours: adherer, partial adherer, overusers, erratic users, partial dropout, dropout



Consequences of nonadherence

- May lead to false conclusions on treatment efficacy
- If a physician is not aware, unnecessary regimen change (disease progression: lack of activity of the drug)
- Increased healthcare costs and waste of resources (more physician visits, higher hospitalization rates, and longer stays)
- Increased toxicities, especially if a patient is taking doses too close together or at the wrong time of day.
- In clinical trials:
 - inaccurate conclusions /dosing recommendations
 - Perceived inferiority of drug when compared to IV formulations

Measurement of adherence-No gold standard

- Several methods exist, but each method shows limitations
- Patient awareness that adherence is being measured may impact the degree of adherence (“Hawthorne effect”)
- Self-report: over-reporting rates of adherence because of a desire to please providers.
- Patient-completed medication diaries: be less susceptible to recall bias because the patient is asked to record each dose as it is taken.

Measurement of adherence: pill counts

- Pill counts have also been shown to overestimate the number of pills actually taken.
- Patients may throw away missed doses to avoid being viewed as nonadherent.
- Pill counts are often used as an alternative or an adjunct to self-report.
- No information concerning the timing of doses, which may be a critical factor in treatment effectiveness in some settings.



Metabolite levels

- Serum or urine drug or metabolite levels: more objective measures of adherence and persistence
- However:
 - do not describe the timing of doses
 - pharmacokinetic variability in drug absorption, distribution, metabolism, and excretion, ranges that are consistent with adherence may be wide
 - accurate measurement of serum or urine drug metabolites is only available for certain drugs

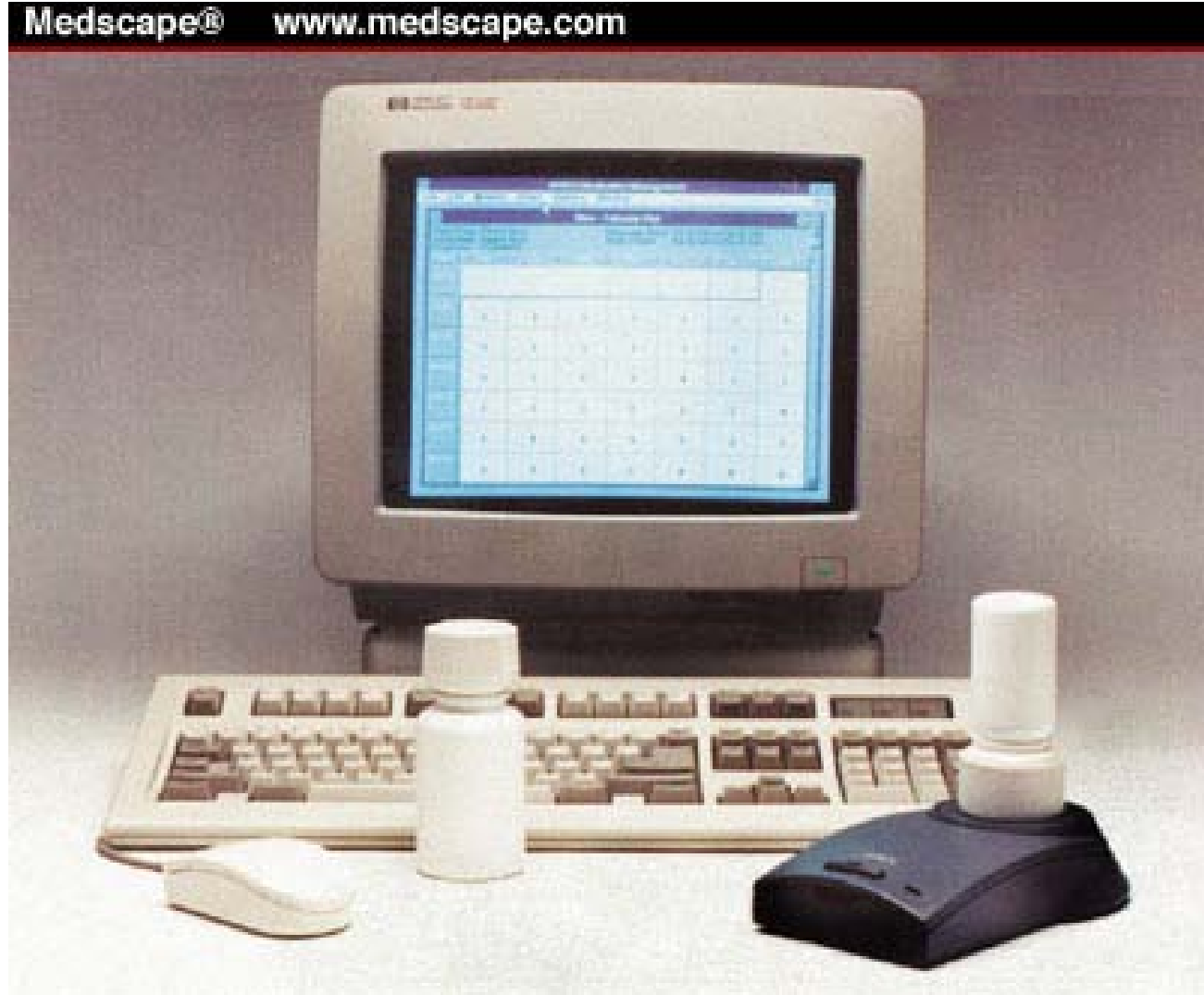


MicroElectronic Monitoring System (MEMS)

- “intelligent” cap on a pill bottle that electronically records every time the cap of the pill bottle is removed.
- MEMS data provide a computerized record of each date and time the bottle is opened.
- MEMS monitoring is considered to be less subject to patient manipulation, however a pill may not be ingested every time the pill bottle is opened.
- MEMS technique is quite expensive and therefore is used primarily in clinical research and is not feasible in many setting

MEMS

Medscape® www.medscape.com



Adherence and persistence

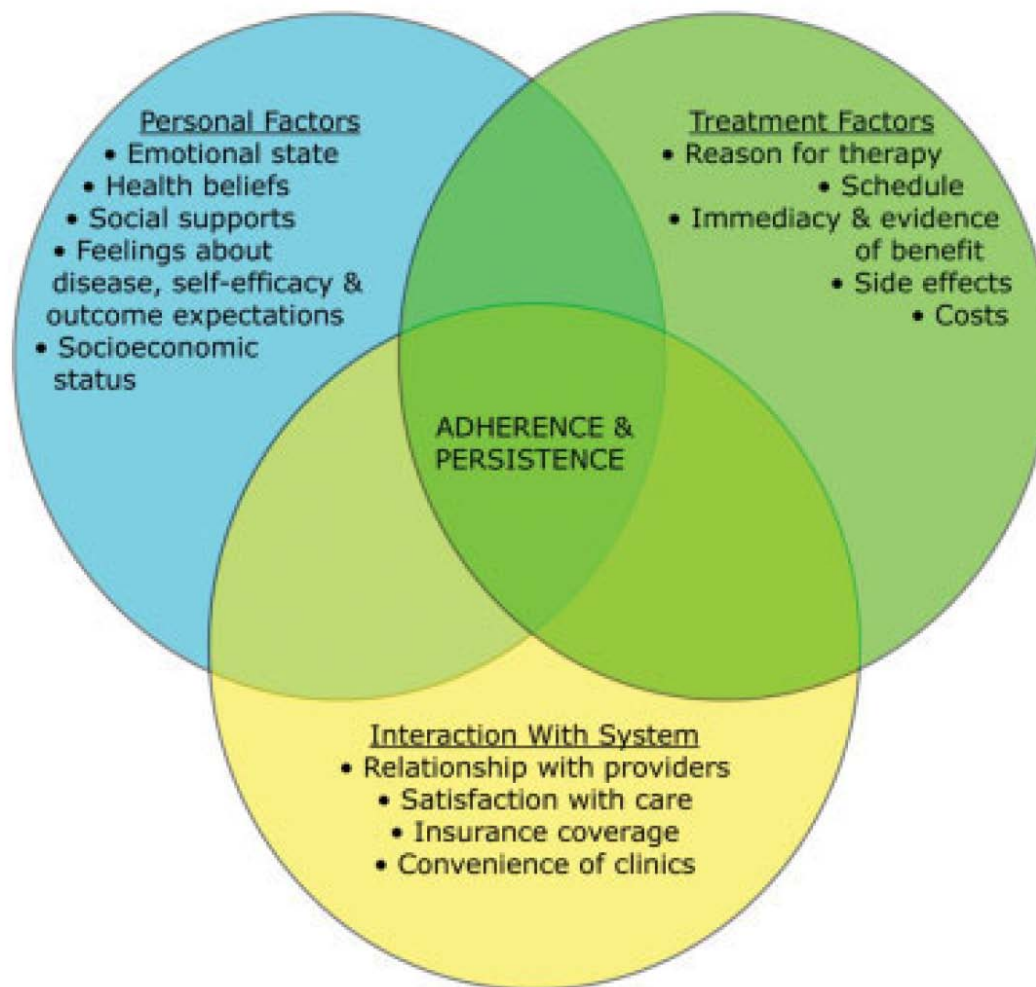
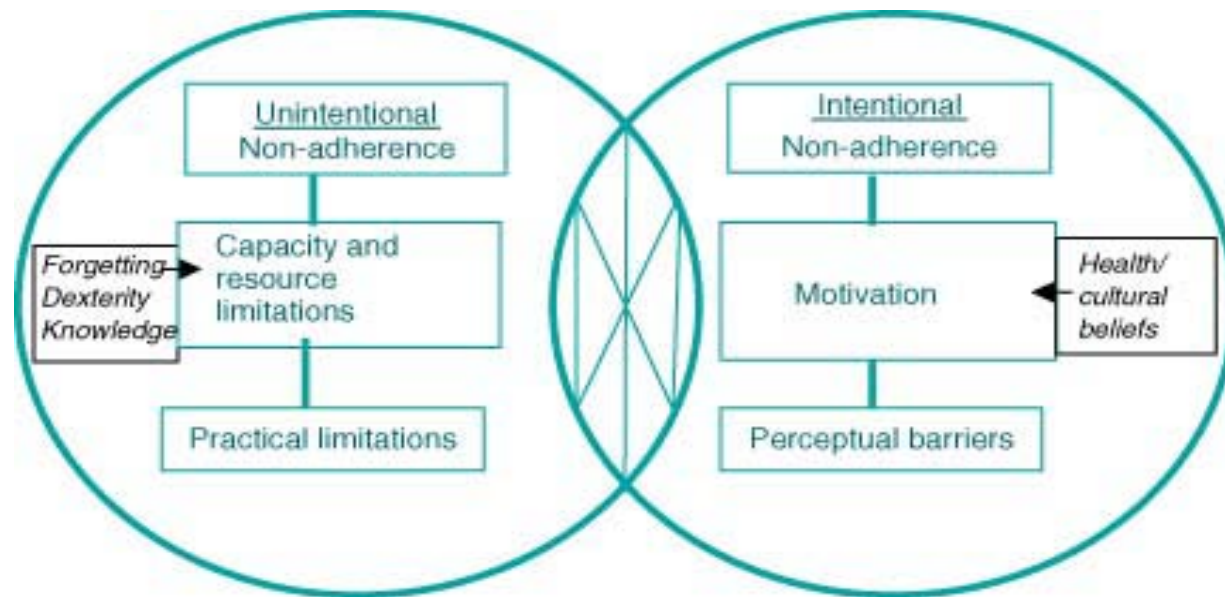
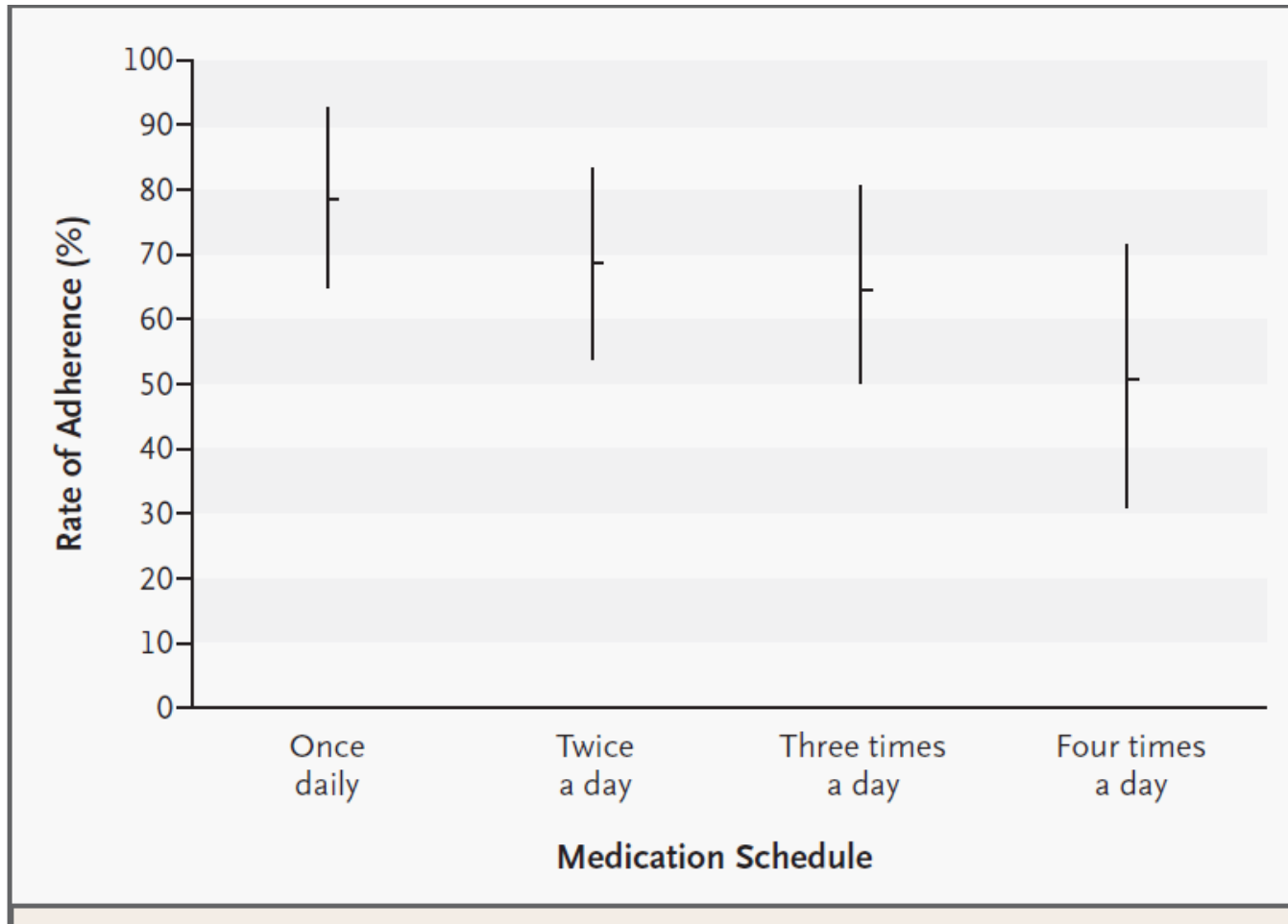


FIGURE 1. Model of Adherence and Persistence.

Unintentional and Intentional non adherence



Adherence according to frequency of doses





Monthly costs of oral drugs

Capecitabine (breast, colon)	\$3,600
Temozolamide (brain)	\$2,200-6,800
Imatinib (CML, GIST)	\$ 3,600
Erlotinib (lung, pancreas)	\$ 3,500
Sorafenib (renal, liver)	\$ 5,600
Dasatinib (ALL, CML)	\$ 6,000
Sunitinib (renal, GIST)	\$ 4,700
Lapatinib (breast)	\$ 3,300

Patient Preferences for Oral Versus Intravenous Palliative Chemotherapy

By Geoffrey Liu, Edmee Franssen, Margaret I. Fitch, and Ellen Warner

- 103 patients evaluated by structured interview-administered scenario-based questionnaire
- Patients were to assume equivalent efficacy, toxicity, clinic visit and blood-work schedules for the two regimens
- 92 preferred oral CT, 10 preferred iv CT, 1 had no preference
- Preferences were not associated with age, sex, site of primary cancer, or previous CT experience

Patient Preferences for Oral Versus Intravenous Palliative Chemotherapy

Table 2. Reasons for Preference for Oral CT (N = 92)

Reason for Preference	Directed Questioning		Likert Statements	
	No	%	No	%
Convenience*	52	57	60	65
Male \leq 65 years	19	70	24	90
Male > 65 years	6	47	7	54
Female \leq 65 years	15	58	16	62
Female > 65 years	12	44	13	48
Problems with IV lines†	51	55	61	66
Male	15	38	20	50
Female	36	68	40	75
Control of CT environment‡	30	33	56	61
Previous IV CT problems‡	25	27	31	34
Travel‡	11	12	n/a	

Abbreviation: n/a, not applicable, as no Likert statement addressed this

Patient Preferences for Oral Versus Intravenous Palliative Chemotherapy

By Geoffrey Liu, Edmee Franssen, Margaret I. Fitch, and Ellen Warner

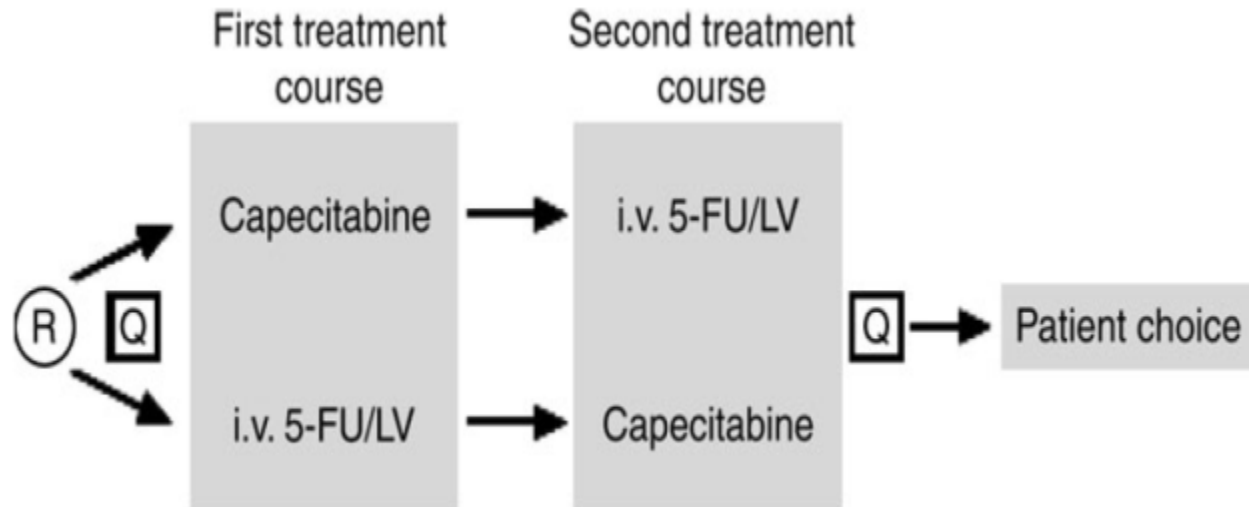
- Regardless of initial preference, 70% of the patients were not willing to accept a lower response rate
- 74% were not willing to accept a shorter duration of response
- 39% of the patients wanted the specific treatment decision made primarily by their physician, 38% primarily by themselves, and 22% shared equally

A randomised cross-over trial comparing patient preference for oral capecitabine and 5-fluorouracil/leucovorin regimens in patients with advanced colorectal cancer

C. Twelves^{1*}, S. Gollins², R. Grieve³ & L. Samuel⁴

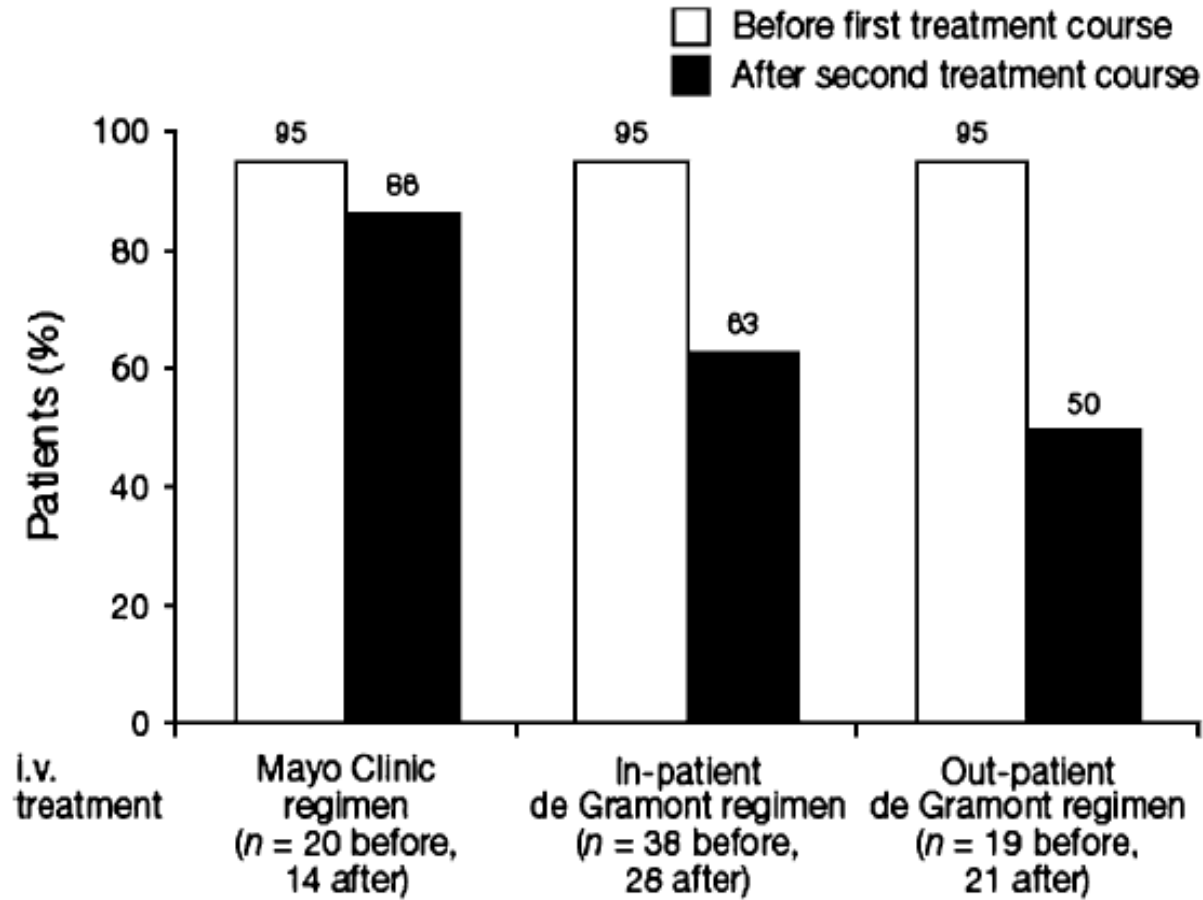
¹University of Leeds, Bradford NHS Trust & Beatson Oncology Centre, Glasgow; ²North Wales Cancer Treatment Centre, Rhyl; ³Walsgrave Hospital, Coventry; ⁴Aberdeen Royal Infirmary, Aberdeen, UK

97 patients with previously untreated metastatic CRC

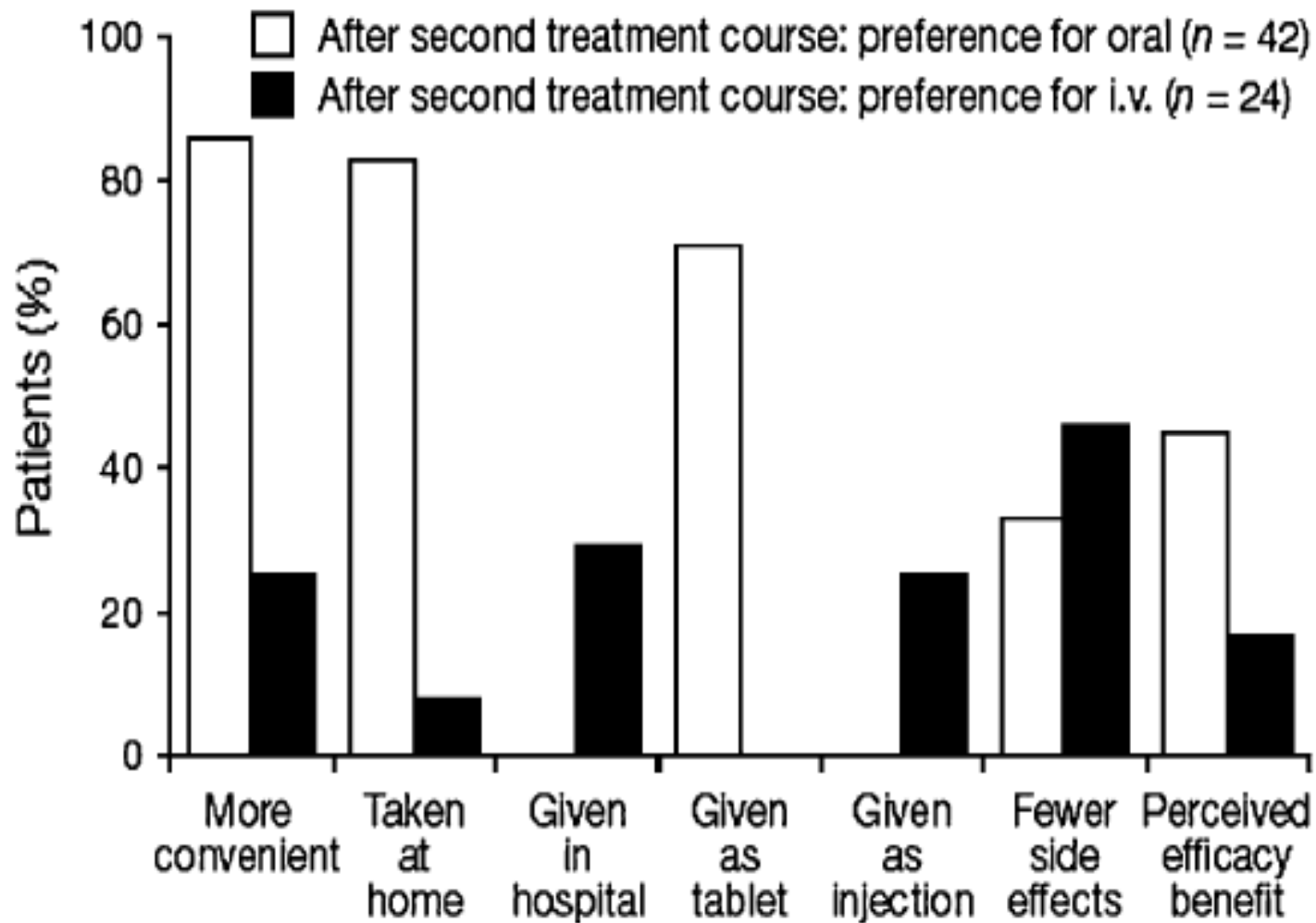


R = randomisation; Q = questionnaire

Patient preference for oral capecitabine or iv 5FU/LV

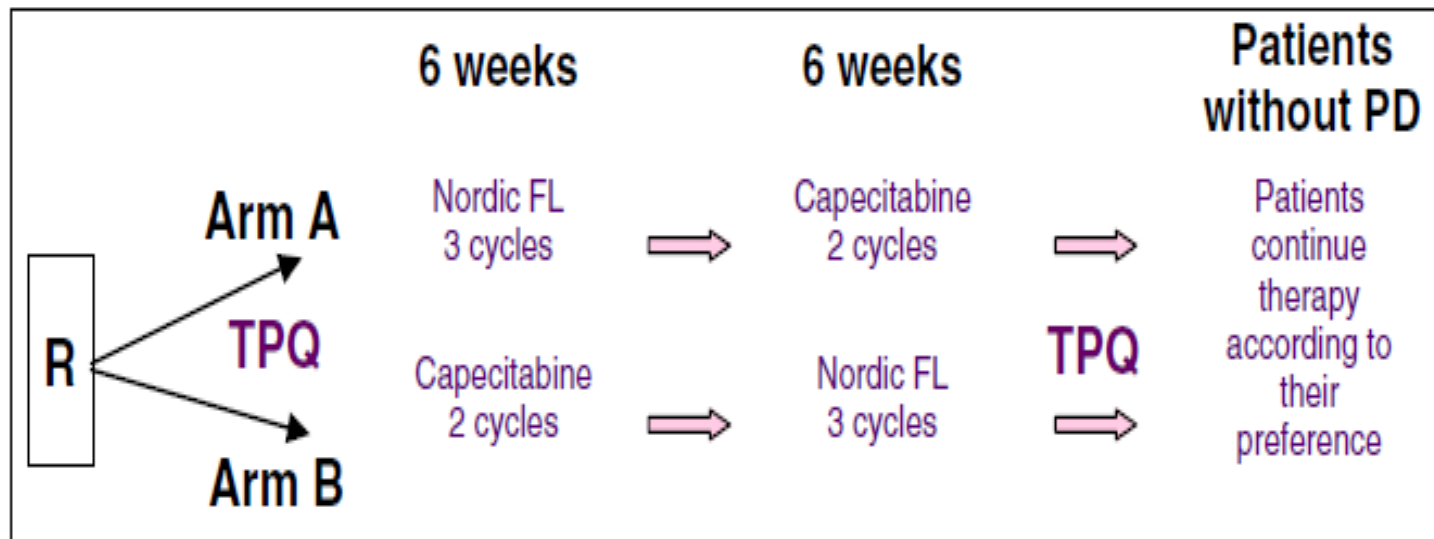


Patient preference for oral capecitabine or iv 5FU/LV



Patient preference for oral or iv therapy

- Randomized cross-over study
- 60 pts with colorectal cancer



Patient preference for oral or iv therapy

Does not interfere with your daily activities	52%
Does not make you vomit	45%
Does not make you feel tired	45%
Does not give diarrhea	43%
Does not make you feel nauseated	43%
Does not affect your mood	43%
Does not cause pain	43%
The medication can be taken at home	39%
Does not cause painful sores in the mouth	34%
The medication is a pill	34%
Does not increase your risk of infection	32%
Medicine is taken at hospital	18%
Medication is given by injection	5%

Patient preference for oral or iv therapy

	Preference for oral	Preference for IV
Arm A	30%	70%
Arm B	46%	54%
Total	39%	61%

- Major reasons for oral preference:
 - “I preferred a pill”
 - “I preferred taking the medication at home”
- Major reasons for iv preference:
 - I had less diarrhea
 - I felt less nauseated
 - I felt less tired
 - Medicine interfered less with my daily activities

Perception that oral anticancer treatments are less efficacious: development of a questionnaire to assess the possible prejudices of patients with cancer

- Pilot test of 12-item questionnaire, to approach patients' perception on efficacy of oral chemotherapy
- 59 Metastatic Breast Cancer Patients who receive oral chemotherapy
- Oral chemotherapy was positively viewed by most patients, perceiving it as :
 - Advantageous (58%)
 - Able to help them feel less ill (77%)
 - Able to reduce the effort of coping with the disease (67%)

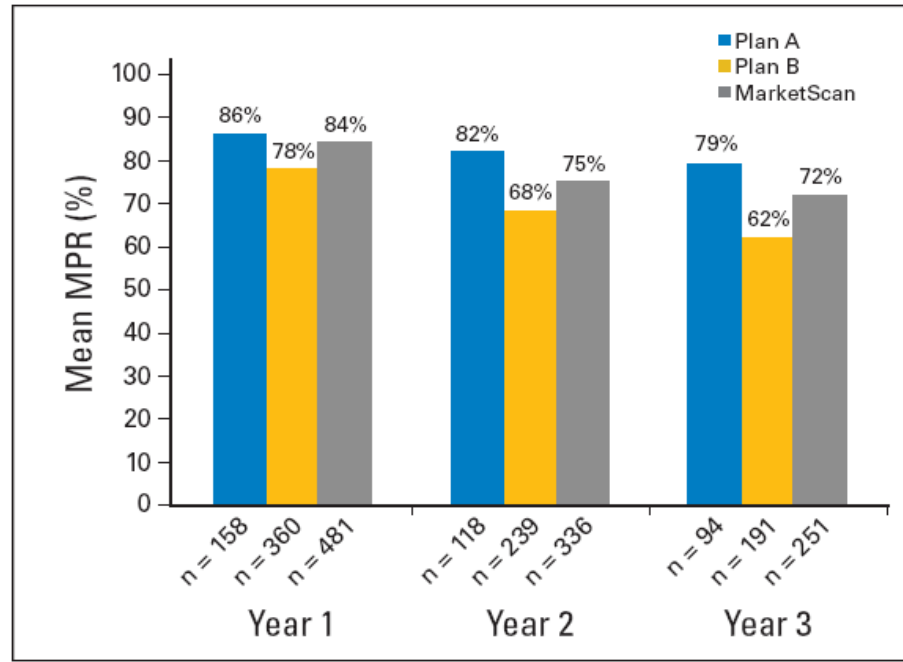
Perception that oral anticancer treatments are less efficacious: development of a questionnaire to assess the possible prejudices of patients with cancer

		Highest				Least
		1	2	3	4	5
<i>What do you expect from an oral chemotherapy?</i>						
Reduction of side effects	57	33	25	14	25	3
Ease of dispensation	55	36	33	24	5	2
A reduction in hospital visits	55	13	22	35	27	4
Avoidance of needle	55	20	16	22	38	4
Other	9	55		11		33
<i>Which is the most negative thing about an oral chemotherapy?</i>						
Reduced efficacy	53	21	19	28	26	6
Mistaken administration	54	24	35	28	9	4
Variability in absorption of medicine	53	43	28	15	11	2
Reduction in hospital visits	53	11	15	23	47	4
Other	9	33		22		44
<i>At the idea of beginning an oral chemo, how do you feel?</i>						
Fearful	53	11	11	40	36	2
Neglected	53	6	13	32	45	4
Free	56	59	25	11	5	
Avoiding an uncomfortable procedure	53	26	47	15	11	
Other	5	20		20		60

Adherence to Initial Adjuvant Anastrozole Therapy Among Women With Early-Stage Breast Cancer

Ann H. Partridge, Andrea LaFountain, Erica Mayer, Brooke S. Taylor, Eric Winer, and Aviva Asnis-Alibozek

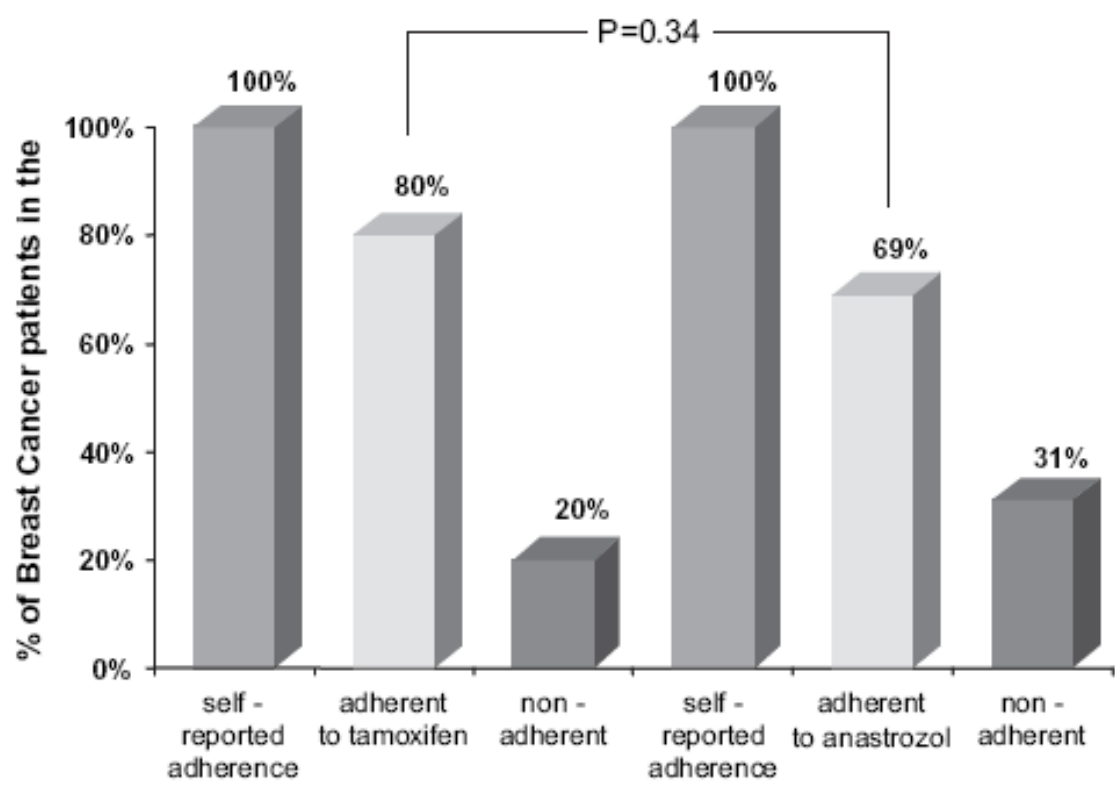
- Longitudinal claims data from three large commercial health programs to estimate adherence
- More than 12,000 women in the databases were found to have new anastrozole prescription claims during the period of study





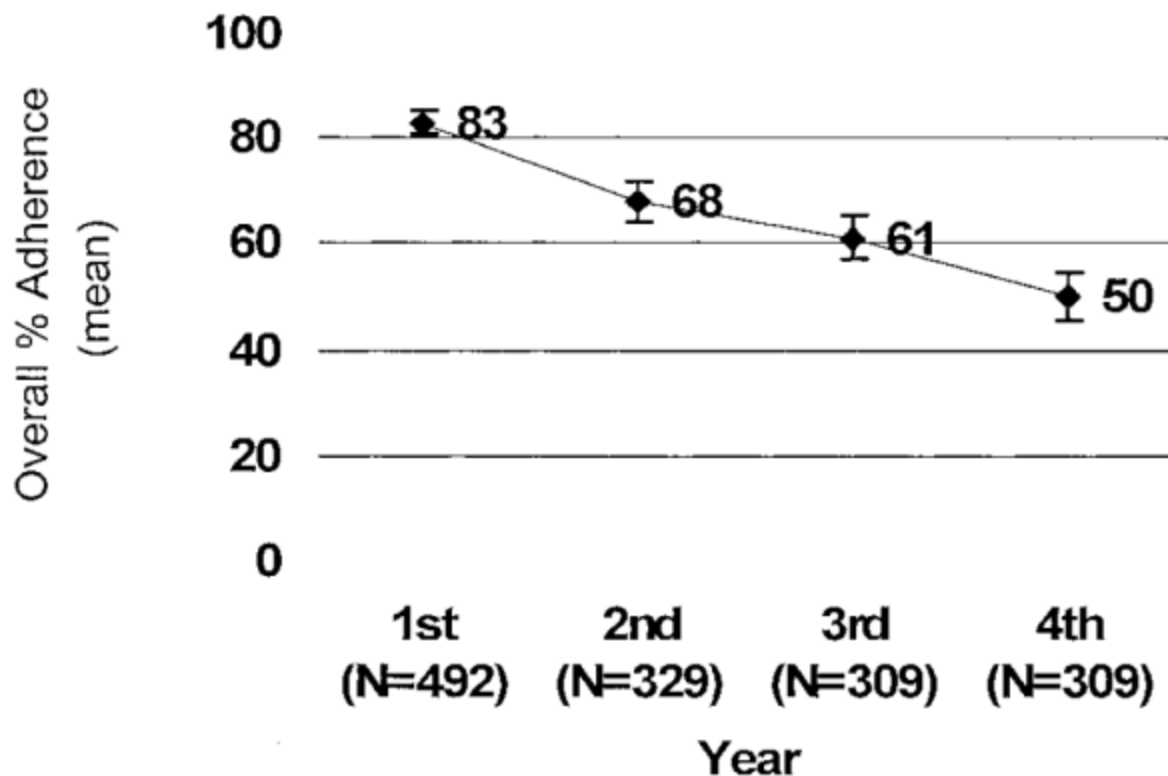
Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer

V. Ziller*, M. Kalder, U.-S. Albert, W. Holzhauser, M. Ziller, U. Wagner & P. Hadji



Nonadherence to Adjuvant Tamoxifen Therapy in Women With Primary Breast Cancer

By Ann H. Partridge, Philip S. Wang, Eric P. Winer, and Jerry Avorn



Association of poor adherence to prescribed tamoxifen with risk of death from breast cancer

- Using the Community Health Index (CHI), the unique patient identifier, a retrospective cohort was derived for all women with incident breast cancer from 1993 to 2002 treated at a regional cancer center.
- Computerized clinical notes, audit records, cancer registry data, and encashed prescription records were linked using CHI with detailed tumor characteristics, deprivation index, co-morbidity, and breast cancer specific mortality.
- 1,633 out of 2,080 (79%) patients were prescribed adjuvant tamoxifen for a median 2.42 years (inter-quartile range 1.04 - 4.89 years), and median adherence to tamoxifen was 93% (inter-quartile range 84% - 100%).
- Increasing age, higher grade, pathological node involvement, estrogen receptor negative/unknown increased the risk of death.
- Patients with less than 70% prescriptions encashed had a significant increase in the risk of death

Adherence and persistence to oral antineoplastic agent over time in BC patients

Study	No. Pts	Oral drug	Adh. or pers. rate	Time period
Lebovits 90	51	Cycloph	53%	6 mo
Waterhouse 93	26	Tam	85-98%	2.9 mo
Murthy02	53	Tam	76%	6 mo
Partridge03	2,378	Tam	77% 1y 50% 4° y	4 y
Grunfeld05	110	Tam	88%	Not stated
Atkins06	131	Tam	55%	Single point
Barron07	2,816	Tam	78% 1y 65% 3.5 y	3.5 y
Thompson07	1,633	Tam	93%	2.4 y
Partridge08	12,391	Anastr.	78-86% 1 y 62-79% 3 y	3 y
Partridge08	161	Capec.	76%	6 cycles

Pharmacokinetic interactions

- Oral delivery necessitate careful evaluation of the factors influencing drug absorption
- Food delays gastric emptying, raises intestinal PH, increases hepatic blood flow and slows GI transit, so it can influence pharmacokinetic profile of some orally administered drugs
- Some orally administered anticancer agents are prodrugs (capecitabine), which require metabolic activation for cytotoxic activity through first-pass effects in the gastrointestinal tract and/or liver before they reach the systemic circulation.

Effect of food on the pharmacokinetics of orally administered anticancer drug

Anticancer agents	Effect of food	Pharmacokinetic parameters affected
Busulfan ¹¹⁴ , fluorouracil ¹¹⁵ , methotrexate ¹¹⁶ and topotecan ¹¹⁷	Delayed absorption (effect on rate)	Change in C_{max} and T_{max}
Altretamine ¹¹⁸ , capecitabine ¹⁴ , chlorambucil ¹¹ , estramustine ¹² , gefitinib ¹¹⁹ , melphalan ¹²⁰ and thioguanine ¹²¹	Decreased absorption (effect on extent)	Change in AUC and C_{max}
Erlotinib ⁴⁴ and tretinoin ¹²²	Increased absorption (effect on extent and/or rate)	Increase in AUC and usually C_{max} and/or T_{max}
Etoposide ¹²³ , imatinib ¹²⁴ , mercaptopurine ¹²⁵ and temozolomide ¹²⁶	Unaffected absorption (no effect on rate or extent)	No significant change in AUC and C_{max}^*

Pharmacokinetic interactions

- The absorption of orally administered anticancer agents that are not prodrugs can also be altered by metabolism within the gastrointestinal tract.
- The activity of cytochrome P450 enzymes (CYP enzymes) in the gut wall is a significant factor that alters the bioavailability of orally administered anticancer agents that are CYP3A substrates
- Drug–food, drug–herb or drug–drug interactions can occur when an orally administered CYP3A substrate is given concomitantly with an inhibitor or inducer of intestinal CYP activity.
- One of the best described examples of a food that alters intestinal CYP3A activity is grapefruit juice. Grapefruit juice is known to be a potent inhibitor of intestinal CYP3A4, and therefore increases the bioavailability of various drugs

Incidence of drug-induced diarrhea with molecular-targeted agents

Agent	Target	All grade (severe)
Erlotinib	HER 1	55%-68% (6%-12%)
Gefitinib	HER 1	40%-60% (3%-8%)
Lapatinib	HER ½	40%-60% (10%- 13%)
Neratinib	HER ½	84%
Sorafenib	VEGFR3/RAF/PDGFRβ	33%
Sunitinib	VEGFR3/RAF/PDGFRβ	20%
Imatinib	BCR-ABL, KIT, PDGFRα	45%
Bortezomib	Proteasome inhibitor	30% (8%-9%)
Flavopiridol	Cyclin-dependent kinase	50%

Pooled analysis of diarrhea events in cancer patients treated with lapatinib

	CTC grade (%)									
	Patients (N)		Lapatinib				No lapatinib			
	L	No L	All	G1/2	G3	G4	All	G1/2	G3	G4
<i>Pooled analysis</i>										
All studies	1417	676	54	45	9	<1	24	20	4	0
Breast	936	477	58	46	11	<1	31	26	5	0
Other solid tumors	481	199	48	44	4	<1	6	5	1	0
Lapatinib monotherapy	926	N/A	51	45	6	<1	N/A	N/A	N/A	N/A
Lapatinib + capecitabine ^a	198	191	65	51	13	1	40	30	10	0
<i>Taxane analysis</i>										
Lapatinib + taxanes ^b	401	286	48	39	9	<1	26	24	1	0

No lapatinib is monotherapy with either hormones (n = 197), capecitabine (n = 191), or paclitaxel (n = 286)

Lapatinib: 1000–1500 mg/day, Paclitaxel: 80 mg/m²/wk or 135–225 mg/m² once every 3 weeks, Capecitabine: 2000–2500 mg/m², Docetaxel: 50–75 mg/m² once every 3 weeks

- First diarrhea event: within 6 days in 42% of L-treated patients
- Similar median duration of diarrhea: 5 days w/ lapatinib; 4 days w/o L

Diarrhea associated with lapatinib treatment: management guidelines-I

- Early identification and intervention is critical
- A patient's baseline bowel patterns should be established
- Physicians and nurses should educate patients on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the physicians

EVALUATION

- Onset and duration
- Number and stool composition
- Presence of fever, dizziness, abdominal cramping
- Dietary profile

Uncomplicated G1-2

Uncomplicated G3-4 or G1-2 with complicating features

MANAGEMENT

- Dietary modifications
- Hydration
- G2: consider holding lapatinib and other cytotoxic treatment
- Consider lapatinib dose reduction

TREATMENT

- standard loperamide dosing: 4 mg initially, then 2 mg q 4 hrs or after every unformed stool

MANAGEMENT

- hospitalization for patients at risk for life-threatening complications
- discontinue lapatinib and other cytotoxic treatment
- iv hydration; octreotide for severe dehydration

TREATMENT

- loperamide 4 mg initially, then 2 mg q 2 hrs or after every unformed stool
- Antibiotics as needed (especially in case of fever or G3-4 neutropenia or symptoms persist > 24 hrs)

Reassess 24 hrs later

DIARRHEA UNRESOLVED

- loperamide 2 mg q 2 hrs + oral antibiotics

Reassess 24 hrs later

DIARRHEA UNRESOLVED

- Start second line agent (eg octreotide)

Symptoms persist

DIARRHEA-FREE FOR 24 HRS

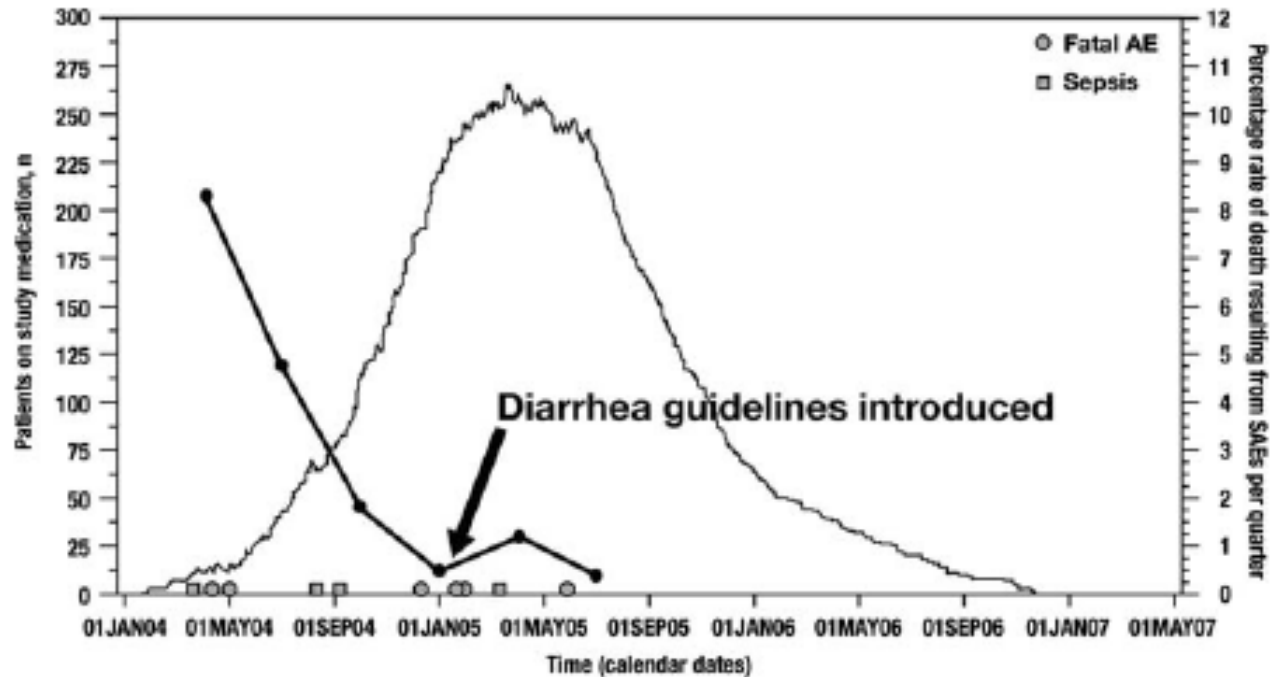
- Discontinue intervention
- Consider reintroducing lapatinib (and other Cytotoxic therapy) at reduced dose

DIARRHEA RESOLVING

- Continue dietary modifications
- gradually add solid foods to diet
- Discontinue loperamide after 12-hrs of symptoms resolution

Modified from Guidelines developed by GSK based on Benson et al. *J Clin Oncol* 2004;22:2918-2

Lapatinib plus paclitaxel study (EGF30001)



- Serious adverse event-related deaths were higher in the combination arm (2.7 vs 0.6%) due to initial lack of experience in managing diarrhea and pharmacokinetic interaction with lapatinib plus paclitaxel¹
- However, incidence of fatal adverse events diminished over time¹
- Reduction was due to implementation of diarrhoea management guidelines^{1,2}

Focus on skin toxicity

- EGFR1 inhibitors are associated with a unique group of skin, hair, and nail toxicities
- EGFR1 inhibitor associated skin toxicity appears to be dose dependent and, in general, is more frequent and of higher grade with mAbs than with TKIs.
- Intriguing relationship with response and survival (cetuximab, erlotinib)
- These toxicities are usually mild; however, they impact negatively on QoL and may lead to dose reduction thus compromising activity

EGFR1 inhibitors associated skin toxicity

- Papulopustular reaction (also variously described as acne or acneiform rash), usually on the face and/or upper trunk
- Severity peaks during the first 1–2 weeks of therapy, stabilizing or improving during the following weeks
- Xerosis (dry skin)
- Pruritus
- Nail/periungual alterations (usually manifested as paronychia)
- Regulatory abnormalities of hair growth (alopecia of the scalp/trichomegaly of the eyelashes/hypertrichosis of the face)
- Telangiectasia (dilatation of capillaries and small blood vessels and hyperpigmentation)



Grade 1



Grade 2



Grade 3



Grade 1



Grade 2



Grade 3

Dermatologic events in patients treated with lapatinib

Skin event	CTC grade, %															
	All L n = 1,417		L n = 926		L + C n = 198		L + P n = 293		No L ^a n = 676		C n = 191		P n = 286		Hormonal n = 199	
	All	G3	All	G3	All	G3	All	G3	All	G3	All	G3	All	G3	All	G3
Rash	43	4	47	3	13	2	50	8	14	<1	8	<1	25	<1	5	<1
Hand-foot syndrome	8	2	<1	<1	54	14	1	<1	14	4	51	14	0	0	0	0
Hair disorder	3	<1	<1	0	<1	0	14	1	16	2	<1	0	37	5	2	0
Dry skin	3	<1	3	<1	2	0	3	0	3	0	2	0	2	0	5	0
Pruritus/Urticaria	3	<1	3	<1	<1	0	5	<1	4	<1	<1	0	7	<1	2	0
Skin disorder	1	0	2	0	<1	0	1	0	<1	<1	2	0	1	<1	0	0
Skin infection	<1	<1	<1	0	<1	<1	0	0	<1	0	0	0	<1	0	0	0
Nail disorder	<1	<1	1	<1	0	0	1	0	<1	0	<1	0	<1	0	<1	0

There were no grade 4 dermatologic events

46% of skin events with lapatinib treatment and 40% with no lapatinib treatment developed early between days 1 to 14 and are usually self-limiting

Most (87%) skin events did not require dose adjustment or treatment interruption

Prevention and management of skin reactions

- Proactive approach is critical
- Advise patients to moisturize dry areas of the body twice a day (eg with thick alcohol-free emollient); minimize exposure to sun light (sunscreen of SPF \geq 30)
- In case of rash, short (maximum of 14 days) course of oral steroids can help patients remain on study therapy; topical corticosteroids, oral semisynthetic tetracyclines
- Pruritic reactions: topical or systemic antihistamines
- Paronychia: antiseptic baths, local potent corticosteroids, and silver nitrate applications; culture-driven, topical, or systemic antibiotics in case of superinfected lesions
- Lapatinib may be interrupted for up to 14 days in case of G3-G4 reactions, or in case of G2 reactions not improved despite therapy and affecting patients QoL

British Oncology Pharmacy Association Position statement on safe practice and the pharmaceutical care of patients receiving oral anticancer chemo

- All cancer patients receiving active anti-cancer treatment should be under the care of specialist oncology/haematology staff.
- The prescribing and dispensing of oral chemotherapy should be carried out and monitored to the same standards as those for parenteral chemotherapy.
- Responsibility for administration of oral drugs ultimately lies with the patient (or a relative or carer) but it is the responsibility of all members of the multidisciplinary oncology/haematology team to ensure as far as practically possible they are adequately prepared for this.
- Effective communication between primary and secondary care and with patients is pivotal to safe and effective treatment
- Other than in exceptional and clearly defined and mutually agreed circumstances, prescribing and dispensing should remain the sole responsibility of the hospital-based oncologist/haematologist and pharmacy respectively.

Patient Education & Information

- Before every treatment cycle, all patients should be seen by a specialist pharmacist or nurse
- The pharmacist/technician handing the drugs to the patient (or relative or carer) must ensure that they fully understand
- How and when to take their medicines. Some patients may find it particularly hard to remember the idea of repeated short courses of treatment with 'gaps' between them.
- What to do in the event of missing one or more doses
- What to do in case of vomiting after taking a dose
- Likely adverse effects and what to do about them
- The need for and how to obtain further supplies
- The role their GP is expected to play in their treatment
- Principles of safe handling, storage and disposal
- That if used, medicine spoons or measures should be used once only and then disposed of safely.
- As much of this information as possible should first be given at the pre-treatment visit and reinforced on subsequent visits.