European Journal of Cancer 54 (2016) 120–130

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Renal function, body surface area, and age are associated with risk of early-onset fluoropyrimidine-associated toxicity in patients treated with capecitabine-based anticancer regimens in daily clinical care

Didier Meulendijks [a,b], J.G. Coen van Hasselt [c], Alwin D.R. Huitema [d], Harm van Tinteren [e], Maarten J. Deenen [a,b], Jos H. Beijnen [d,f], Annemieke Cats [g], Jan H.M. Schellens [a,b,f,*]

[a] *Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[b] *Division of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[c] *Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands*
[d] *Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[e] *Department of Biometrics, The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[f] *Faculty of Science, Department of Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands*
[g] *Division of Gastroenterology and Hepatology, Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*

Received 14 July 2015; received in revised form 11 October 2015; accepted 18 October 2015
Available online 4 January 2016

KEYWORDS
Fluoropyrimidine-associated toxicity;
Capecitabine;
Safety;
adverse events;
Toxicity

Abstract ***Background:*** The objective of this analysis was to determine the factors associated with early onset treatment-related toxicity in patients treated with capecitabine-based anticancer regimens in daily clinical care.
Patients and Methods: A total of 1463 patients previously included in a prospective cohort study and treated with standard-of-care capecitabine-based anticancer regimens (monotherapy or combined with other chemotherapy or radiotherapy) were analysed. Logistic regression models were developed to investigate associations between patient- and treatment-related factors and occurrence of early – i.e. cycle one or two – severe (grade $\geq$ 3) treatment-related toxicity, toxicity-related hospitalisation, and toxicity-related treatment discontinuation. Performance of models was evaluated using receiver-operating characteristic (ROC) curves and

* *Corresponding author:* Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Tel.: +31 20 512 2446; fax: +31 20 512 2572.
E-mail address: j.schellens@nki.nl (J.H.M. Schellens).

http://dx.doi.org/10.1016/j.ejca.2015.10.013

internal validity was explored using bootstrap analysis.
Results: Among 1463 patients included, 231 patients (16%) experienced early severe toxicity, 132 patients (9%) were hospitalised for toxicity, and 146 patients (10%) discontinued treatment for toxicity; in total, 321 patients (22%) experienced any early toxicity-related adverse outcome. Predictors of early grade ≥3 toxicity, after adjustment for treatment regimen, were renal function (odds ratio [OR] 0.85 per 10 ml/min/1.73 m^2, $p = 0.0007$), body surface area (BSA) (OR 0.33 per m^2, $p = 0.0053$), age (OR 1.14 per decade, $p = 0.0891$), and elevated pre-treatment uracil concentrations (OR 2.41 per 10 ng/ml, $p = 0.0046$). Age was significantly associated with fatal treatment-related toxicity (OR 5.75, $p = 0.0008$). Area under the ROC curve (AUC) of a model to predict early grade ≥3 toxicity was 0.704 (95% confidence interval 0.666–0.743, optimism-corrected AUC 0.690).
Conclusion: Renal function, BSA, and age, in addition to pre-treatment uracil, are associated with clinically relevant differences in risk of early severe toxicity in patients treated with capecitabine in routine clinical care.

Key message

In patients treated with capecitabine in daily clinical care, renal function, body surface area, and age, in addition to dihydropyrimidine dehydrogenase deficiency, are associated with clinically relevant differences in risk of early severe toxicity. These factors should be considered in evaluating the benefit–risk balance of treatment for individual patients, in order to avoid severe and potentially lethal early onset toxicity.

1. Introduction

The orally administered 5-fluorouracil (5-FU) prodrug capecitabine has an important role in the treatment of gastric, colorectal, breast, and head and neck cancers. Capecitabine is used as a single agent, in combination with other chemotherapeutic agents, such as platinum agents and taxanes, or in combination with radiotherapy. A substantial proportion of patients experience severe treatment-related toxicity, including gastrointestinal, haematological, and cardiac toxicity, and hand–foot syndrome (HFS) [1]. The incidence of severe treatment-related toxicity differs between treatment regimens. In the pivotal studies of capecitabine monotherapy in metastatic colorectal cancer, 30–40% of the patients experienced severe treatment-related toxicity [1,2]. On the other hand, frequencies of 60–70% are common for women with metastatic breast cancer treated with capecitabine plus docetaxel [3]. Treatment-related hospitalisation rates can be substantial and range between 10% and 28% in phase III studies [1,3]. Furthermore, an estimated 0.5–1.0% of the patients treated with capecitabine-based regimens experiences fatal treatment-related toxicity [4]. Thus, treatment-related toxicity has a large impact on patient safety and quality of life. In addition, it is associated with an estimated ~$2700 increase in health care costs per patient treated with 5-FU [5].

The best-known biochemical cause of intolerance to fluoropyrimidines is deficiency of the key 5-FU metabolic enzyme dihydropyrimidine dehydrogenase (DPD), which explains up to half of the fluoropyrimidine-associated toxicities [6]. Several studies have indicated that also other patient-related factors such as age, sex, and body composition might contribute to risk of treatment-related toxicity in patients treated with 5-FU [7,8]. Little is known, however, about the impact of patient-related factors on risk of capecitabine-associated toxicity in routine clinical practice. Knowledge about the factors associated with risk of toxicity is crucial in order to evaluate the risk–benefit balance of treatment for individual patients.

To investigate the impact of patient- and treatment-related factors as predictors of early onset treatment-related toxicity, we analysed the safety data of a large population of patients enrolled previously in a prospective cohort study and treated with capecitabine-based anticancer regimens in daily clinical care.

2. Patients and methods

A synopsis of the methods is provided here (full details in Appendix).

2.1. Patients

Patients were treated previously in a prospective cohort study with standard-of-care capecitabine-based anticancer regimens [9]. Toxicity was monitored and recorded according to CTC-AE v3.0.

2.2. End-points

Three end-points occurring during the first two treatment cycles were investigated: severe (grade ≥ 3) treatment-related toxicity, any toxicity resulting in hospitalisation, and any toxicity resulting in permanent discontinuation of treatment. In addition, we investigated the factors associated with individual types of fluoropyrimidine-associated toxicity (e.g. gastrointestinal and haematological) and with fatal toxicity, and explored associations with dose reductions and unplanned treatment interruptions.

2.3. Data collection

Data were collected on patient and treatment characteristics, and on the following treatment-related toxicities: gastrointestinal toxicity (diarrhoea and mucositis/stomatitis), haematological toxicity (neutropenia, leucocytopenia, and thrombocytopaenia), HFS, and cardiac toxicity. Toxicities were dichotomised as absent to mild (CTC-AE grade 0–2) versus severe (grade 3–5, i.e. dose limiting to fatal), except cardiac toxicity which was dichotomised as grade 0–1 versus grade 2–5, since grade 2 cardiac toxicity often results in discontinuation of treatment with capecitabine. Treatment regimens were categorised as follows: capecitabine monotherapy, capecitabine-based chemoradiotherapy, capecitabine plus platinum agent, capecitabine plus taxane, capecitabine-based triplet combination, and capecitabine plus other drug (detailed in Table S1, Appendix). We previously investigated the association between dihydropyrimidine dehydrogenase (*DPYD*) genotypes and fluoropyrimidine-associated toxicity in the same cohort of patients and found *DPYD* c.2846A>T and c.1679T>G to be clinically relevant predictors of fluoropyrimidine-associated toxicity (submitted manuscript). These variants were therefore included *a priori* as a covariable in all analyses. Pre-treatment serum uracil concentrations, which we also previously found to be strongly associated with risk of fluoropyrimidine-associated toxicity (submitted manuscript), were available for 507 patients and the association with toxicity in relation to other identified predictors was estimated in this subset of patients.

Table 1
Patient and disease characteristics.

Characteristics	Overall population, $N = 1463$
Age (years)	
Median (IQR)	61 (53–68)
Range	21–89
Sex	
Female	820 (56%)
Male	643 (44%)
Race	
Caucasian	1406 (96%)
African	17 (1%)
Other	40 (3%)
Previous chemotherapy	
No	1124 (77%)
Yes	339 (23%)
5-FU or capecitabine based	150 (10%)
Other	214 (15%)
BSA (m^2)	
Median (IQR)	1.86 (1.72–2.00)
Range	1.10–2.70
eGFR (ml/min/1.73 m^2)	
Median (IQR)	89 (79–101)
Range	16–150
Tumour type	
Colorectal (locally advanced)	509 (35%)
Colorectal (metastatic)	285 (19%)
Breast (locally advanced)	104 (7%)
Breast (metastatic)	252 (17%)
Gastric cancer	184 (13%)
Other	129 (9%)
Treatment regimen[a]	
Capecitabine monotherapy	434 (30%)
Capecitabine plus platinum	382 (26%)
Capecitabine plus radiotherapy	444 (30%)
Capecitabine triplet combination	116 (8%)
Capecitabine plus taxane	65 (4%)
Capecitabine plus other	22 (2%)
DPYD polymorphisms[b]	
*DPYD**2A heterozygous	18 (1%)
c.2846A>T heterozygous	17 (1%)
c.1679T>G heterozygous	2 (0.1%)

Abbreviations: BSA = body surface area; IQR = interquartile range; eGFR = estimated glomerular filtration rate (according to MDRD-4 [11]); *DPYD* = dihydropyrimidine dehydrogenase; 5-FU = 5-fluorouracil.

[a] The administered treatment regimens are described in detail in the Appendix.

[b] Seven carriers of the c.2846A>T allele (1%) and two of the c.1679T>G allele (0.1%) were identified retrospectively and were treated with a full starting dose of capecitabine. The 18 patients with the *DPYD**2A allele were identified upfront and treated with an initially 50% reduced dose.

2.4. Data analysis

Logistic regression models were developed to determine which patient- and treatment-related factors were associated with early onset severe toxicity, toxicity-related hospitalisation, and toxicity-related treatment discontinuation. The type of treatment regimen was included *a priori* as a covariable in the models. Since the planned starting dose of capecitabine was highly collinear with type of treatment regimen and had no relevant effect on effect estimates after inclusion of treatment regimen in the models, starting dose was not included in the models. The predictive value of the following candidate factors was subsequently evaluated: age, sex, body surface area (BSA), body mass index, body weight, lean body mass [10], race, tumour type, previous treatment with chemotherapy, estimated glomerular filtration rate (eGFR, according to MDRD-4, expressed per 1.73 m^2 [11]), and germ line *DPYD* mutations (c.2846A>T and c.1679T>G). Variables were selected by stepwise backward elimination based on the Akaike information

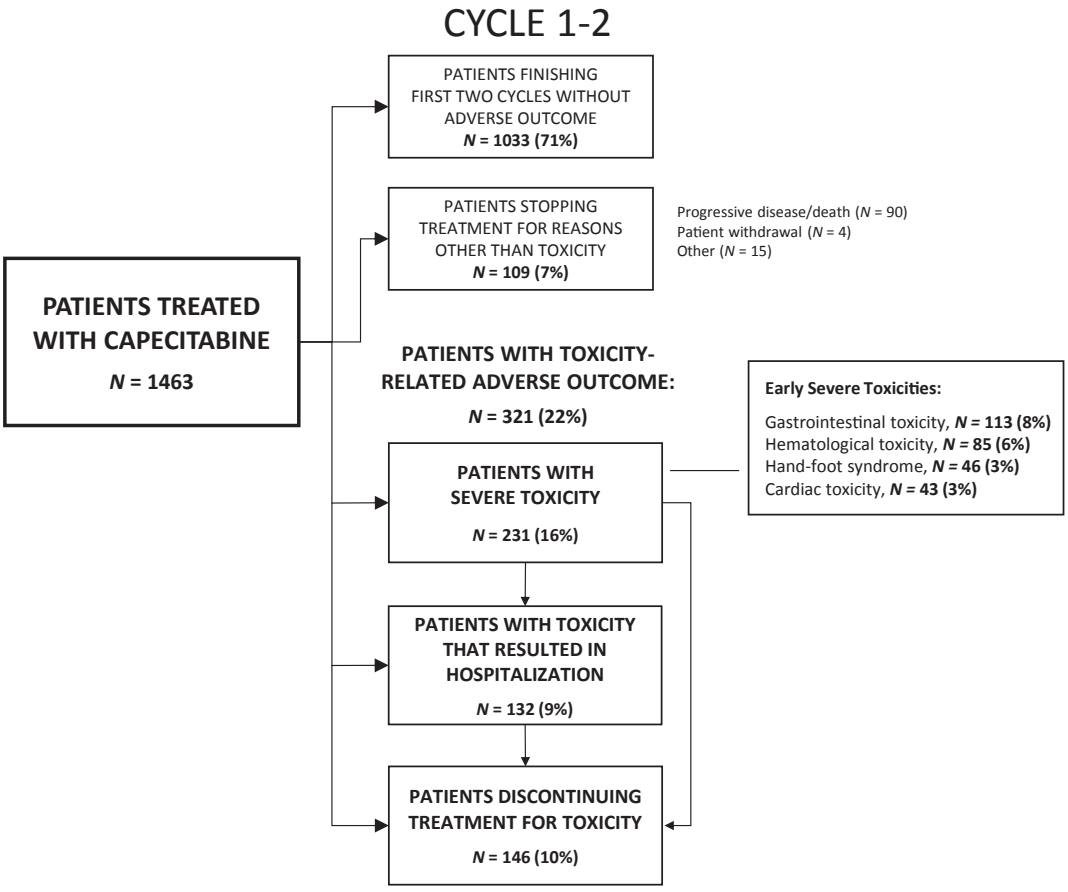


Fig. 1. Early toxicity-related adverse outcomes in the overall population. Frequencies of early onset (cycles 1 and 2) treatment-related severe toxicities in the overall population of patients treated with capecitabine-based chemo- or chemoradiotherapy.

criterion (AIC). Only factors that increased AIC upon elimination were kept in the model. The predictive value of pre-treatment uracil concentrations was assessed separately in the cohort of patients for whom concentrations had been measured (n = 507), by adding pre-treatment uracil concentration as a covariable to the final model developed on the complete dataset. For factors remaining in the final model after excluding uninformative variables, odds ratios (ORs), 95% confidence intervals (CIs), and corresponding p values were reported. The reported OR for continuous variables corresponds with the risk associated with 10 or 50 units increase in the respective variable, as indicated.

Interactions were assessed, among and between identified predictors and type of treatment regimen. Predicted risks of severe toxicity were plotted as a function of the identified predictors in a Trellis plot. To explore discriminative performance of the models, the area under the receiver-operating characteristic curve (AUC) of the receiver-operating characteristic (ROC) curve was determined. CIs for AUC were calculated using DeLong method [12]. Internal validity was assessed in 1000 bootstrap samples to estimate the optimism-corrected AUC using the 'validate' function from package 'rms' in R. All statistical analyses were performed in R statistical software v3.1.1 [13]. The threshold for significance was set at $p < 0.05$. All p values are reported as derived from the analysis, without correction for multiple testing.

3. Results

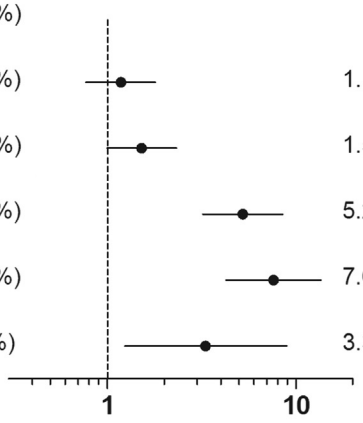
A total of 1463 patients treated with capecitabine-based chemo- or chemoradiotherapy in study NCT00838370 were included in the analysis (Table 1).

3.1. Gastrointestinal toxicity is the most relevant early onset capecitabine-associated toxicity

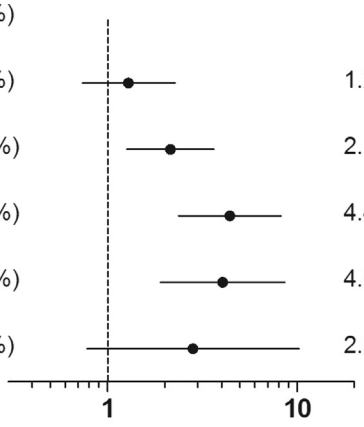
In total, 321 patients (22%) experienced an early toxicity-related adverse outcome (Fig. 1). Two hundred thirty-one patients (16%) experienced early severe toxicity, the most common types being gastrointestinal toxicity (8%), followed by haematological toxicity (6%), HFS (3%), and cardiac toxicity (3%). Six patients (0.4%) suffered fatal treatment-related toxicity, which was associated with (severe) gastrointestinal toxicity in all six cases, and with additional severe haematological toxicity

Table 2
Effect of treatment regimen on risk of early (cycle 1–2) adverse outcomes.

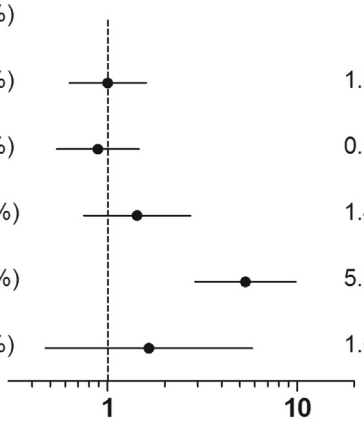
Severe treatment-related toxicity	*N* patients	*N* events	OR (95% CI)	*p* value
Capecitabine monotherapy	434	44 (10%)	(reference)	-
Capecitabine-based chemoradiotherapy	444	52 (12%)	1.18 (0.77-1.80)	0.4554
Capecitabine plus platinum	382	56 (15%)	1.52 (1.00-2.32)	0.0505
Capecitabine-based triplet combinations	116	43 (37%)	5.22 (3.20-8.51)	<0.0001
Capecitabine plus taxane	65	30 (46%)	7.60 (4.26-13.55)	<0.0001
Capecitabine plus other	22	6 (27%)	3.32 (1.24-8.93)	0.0173



Toxicity-related hospitalization	*N* patients	*N* events	OR (95% CI)	*p* value
Capecitabine monotherapy	434	23 (5%)	(reference)	-
Capecitabine-based chemoradiotherapy	444	30 (7%)	1.29 (0.74-2.27)	0.3658
Capecitabine plus platinum	382	41 (11%)	2.15 (1.26-3.65)	0.0047
Capecitabine-based triplet combinations	116	23 (20%)	4.42 (2.38-8.22)	<0.0001
Capecitabine plus taxane	65	12 (18%)	4.05 (1.90-8.60)	0.0003
Capecitabine plus other	22	3 (14%)	2.82 (0.78-10.23)	0.1145



Toxicity-related treatment discontinuation	*N* patients	*N* events	OR (95% CI)	*p* value
Capecitabine monotherapy	434	38 (9%)	(reference)	-
Capecitabine-based chemoradiotherapy	444	39 (9%)	1.00 (0.63-1.60)	0.9882
Capecitabine plus platinum	382	30 (8%)	0.89 (0.54-1.46)	0.6424
Capecitabine-based triplet combinations	116	14 (12%)	1.43 (0.75-2.74)	0.2813
Capecitabine plus taxane	65	22 (34%)	5.33 (2.89-9.83)	<0.0001
Capecitabine plus other	22	3 (14%)	1.65 (0.47-5.81)	0.4391



OR = odds ratio; CI = confidence interval

in three cases. One hundred thirty-two patients (9%) were hospitalised for toxicity. Most strongly related to risk of hospitalisation were gastrointestinal toxicity (OR 43.5, 95% CI 25.7–73.8, $p < 1 \times 10^{-15}$), haematological toxicity (OR 17.7, 95% CI 9.67–32.5, $p < 1 \times 10^{15}$) and cardiac toxicity (OR 17.0, 95% CI 7.81–37.0, $p < 1 \times 10^{-15}$). HFS was not associated with hospitalisation (OR 1.02, 95% CI 0.29–3.55, $p = 0.975$). One hundred forty-six patients (10%) discontinued treatment due to toxicity before cycle three. Toxicity-related treatment discontinuation was most strongly related to cardiac toxicity (OR 17.4, 95% CI 8.91–34.1, $p < 1 \times 10^{-15}$), followed by gastrointestinal toxicity (OR 7.33, 95% CI 4.60–11.7, $p < 1 \times 10^{-15}$), HFS (OR 6.11, 95% CI 3.03–12.3, $p < 1 \times 10^{-6}$), and haematological toxicity (OR 3.76, 95% CI 2.13–6.63, $p < 1 \times 10^{-5}$).

3.2. Risk of early adverse outcome differs strongly between treatment regimens but not tumour types

The frequencies and risks of early toxicity-related outcomes differed strongly between treatment regimens (Table 2, risks calculated in univariable analysis). Risk of early toxicity was generally higher with combination regimens than with monotherapy or chemo-radiotherapy, both for global toxicity and for most individual types of toxicity (Appendix Table S2). We investigated the effect of tumour type because of the possibility that patients with certain tumour types or disease stages could generally be in a poorer health state. However, tumour types were not associated with risk of toxicity after adjustment for treatment regimen ($p = 0.1596$, likelihood-ratio test).

Table 3
Patient-related factors associated with early (cycle 1–2) adverse outcomes in the overall population.

Overall population ($N = 1463$)	N events (%)	OR	95% CI (lower bound)	95% CI (upper bound)	p Value
Global severe toxicity	231 (16)				
Age (per 10 years)		1.14	0.98	1.34	0.0891
BSA (per m^2)		0.33	0.15	0.72	0.0053
Renal function (per 10 ml/min/1.73 m^2)[a]		0.85	0.78	0.94	0.0007
Pre-treatment uracil concentrations (per 10 ng/ml)[b]		2.41	1.31	4.44	0.0046
DPYD polymorphisms (heterozygous versus wild type)[c]		3.00	1.01	8.63	0.0488
Severe gastrointestinal toxicity	113 (8)				
Age (per 10 years)		1.30	1.05	1.61	0.0167
BSA (per m^2)		0.27	0.10	0.76	0.0128
Renal function (per 10 ml/min/1.73 m^2)[a]		0.82	0.73	0.93	0.0014
Race (African versus other)		3.55	0.95	13.2	0.0593
Pre-treatment uracil concentrations (per 10 ng/ml)[b]		3.25	1.47	7.19	0.0037
Severe haematological toxicity	85 (6)				
Renal function (per 10 ml/min/1.73 m^2)[a]		0.89	0.78	1.02	0.0995
DPYD polymorphisms (heterozygous versus wild type)[c]		5.28	1.03	27.1	0.0462
Toxicity-related hospitalisation	132 (9)				
BSA (per m^2)		0.18	0.07	0.47	0.0016
Renal function (per 10 ml/min/1.73 m^2)[a]		0.84	0.76	0.94	0.0016
Pre-treatment uracil concentrations (per 10 ng/ml)[b]		3.11	1.51	6.43	0.0022
DPYD polymorphisms (heterozygous versus wild type)[c]		2.93	1.16	7.38	0.0231
Early discontinuation of treatment	146 (10)				
Age (per 10 years)		1.29	1.09	1.53	0.0067
BSA (per m^2)		0.28	0.11	0.70	0.0036
Fatal treatment-related toxicity[d]	6 (0.4)				
Age (per 10 years)		5.75	2.07	15.93	0.0008
Renal function (per 10 ml/min/1.73 m^2)[a]		0.64	0.41	0.99	0.0433
BSA (per m^2)		0.35	0.01	19.65	0.6071
Pre-treatment uracil concentrations (per 10 ng/ml)[b]		7.00	2.08	23.6	0.0017
Any early adverse outcome[e]	321 (22)				
Age (per 10 years)		1.16	1.01	1.32	0.0340
BSA (per m^2)		0.32	0.16	0.63	0.0010
Renal function (per 10 ml/min/1.73 m^2)[a]		0.90	0.84	0.98	0.0144
Pre-treatment uracil concentrations (per 10 ng/ml)[b]		1.95	1.11	3.42	0.0198
DPYD polymorphisms (heterozygous versus wild type)[c]		2.31	0.84	6.33	0.1050

BSA = body surface area; OR = odds ratio; CI = confidence interval; *DPYD* = dihydropyrimidine dehydrogenase.

[a] Estimated glomerular filtration rate according to MDRD-4. Missing values were imputed using a linear regression model containing age (−0.60 per decade), sex (−1.03 for female sex), and BSA (−2.77 per m^2) as covariables ($r^2 = 0.12$). The estimated effect of renal function before imputation was found to be similar as after imputation (OR 0.85, 95% CI 0.77–0.94, $p = 0.0011$).

[b] The effect of pre-treatment uracil concentration was tested in the subset of patients of whom they were measured ($n = 507$), with adjustment for the other listed covariables (except for fatal toxicity which was tested in univariable analysis).

[c] c.2846A>T and c.1679T>G, combined.

[d] Univariable models.

[e] Any severe (grade ≥ 3) toxicity, any toxicity-related hospitalisation, or permanent discontinuation of treatment due to toxicity.

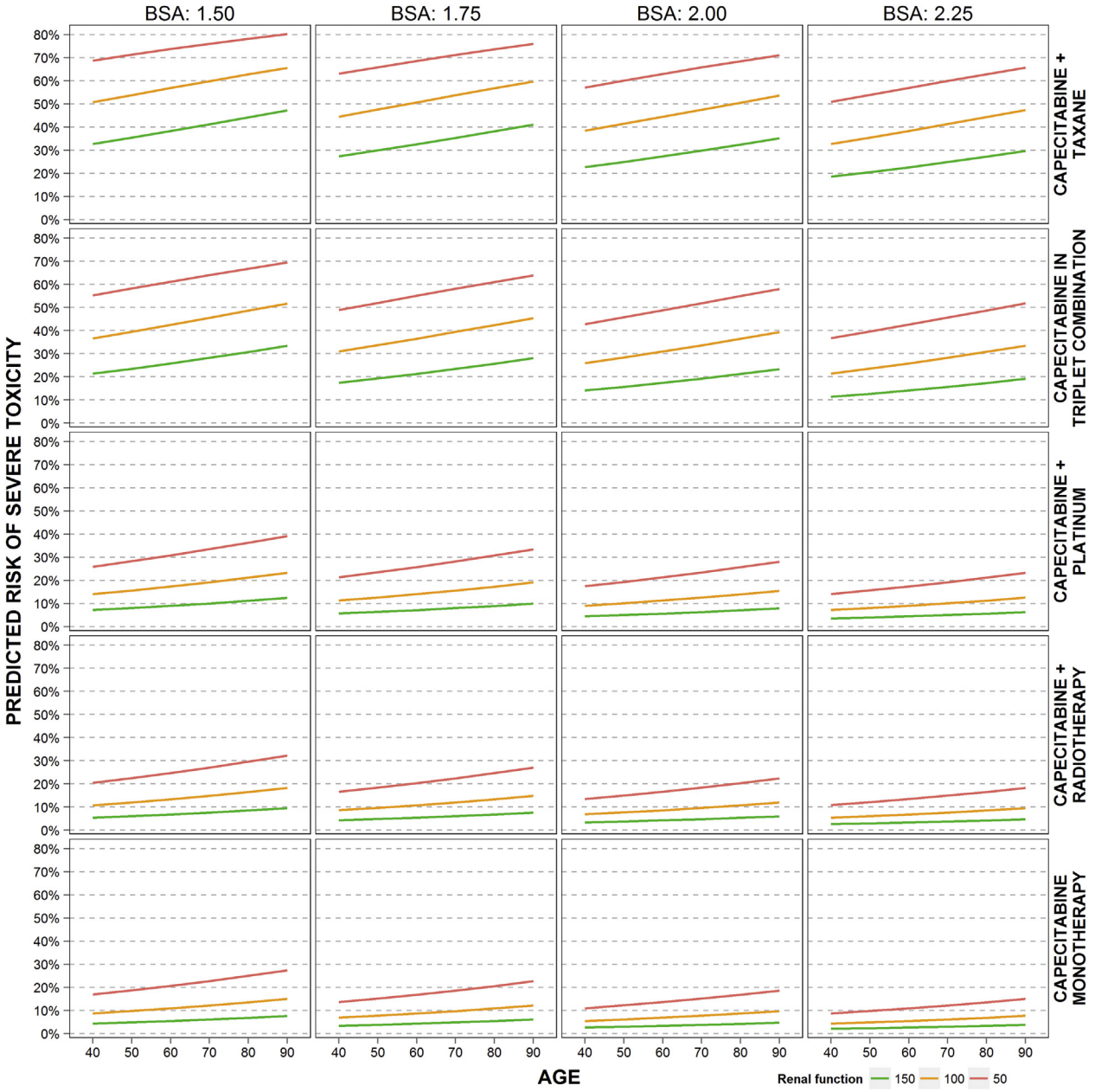


Fig. 2. Predicted risk of any early severe toxicity as a function of age, renal function, body surface area, and treatment regimen. The predicted risk of (any) cycle 1 or 2 severe treatment-related toxicity, based on the developed logistic model, expressed as a percentage, is shown.

3.3. Renal function, BSA, and age are associated with early onset severe toxicity

In the final multivariable models, renal function, BSA, and age were predictive of global severe toxicity, as was DPD deficiency, detected either as *DPYD* polymorphisms or elevated pre-treatment uracil concentrations (Table 3). Age improved AIC but was not statistically significant in the final model for global severe toxicity. The relationships with severe toxicity of the continuous variables renal function, BSA, and age were linear in partial residual plots and there was no evidence for non-linearity ($p > 0.2$). There was no evidence for dose capping at higher BSA (not shown). There were no interactions between identified predictors and patient-related factors or between the identified predictors and treatment regimens (details not shown). Fig. 2 shows the relation between identified predictors and risk of early severe toxicity.

When renal function was removed from the final multivariable model shown in Table 3, age was more strongly associated with global severe toxicity (OR 1.23, 95% CI 1.06–1.42, $p = 0.0063$), suggesting that age and renal function are associated and that part of the effect

of higher age might be related to lower renal function. To further differentiate between renal function and other patient-related factors, additional analyses were performed in which first a model was built using all patient characteristics, and subsequently either GFR (MDRD-4) or serum creatinine concentration was added to this model. These analyses confirmed the independent predictive value of renal function (Table S4).

Sex was not associated with global toxicity (OR 1.09 when added to the final model). However, when BSA was removed, there was a trend toward increased risk of toxicity for women (OR 1.36, 95% CI 0.97–1.91, $p = 0.0722$), suggesting that this effect of sex was related to BSA. We also investigated the effect of the independent variables by determining associations with toxicity end-points for each independent variable separately, with adjustment for treatment regimen only. These analyses revealed similar effect estimates as in the multivariable analyses, and confirmed the predictive effect of age, BSA, renal function, and DPD deficiency (Table S3).

Age, renal function, BSA, and pre-treatment uracil concentrations were strongly associated with severe gastrointestinal toxicity, and there was some evidence for an association with African race (OR 3.55, 95% CI 0.95–13.2, $p = 0.0593$). However, only a small number of patients of African race were treated in the study ($n = 17$). Age was the only factor that was significantly associated with interruption of chemotherapy in the first cycle (OR 1.23, 95% CI 1.04–1.47, $p = 0.0181$).

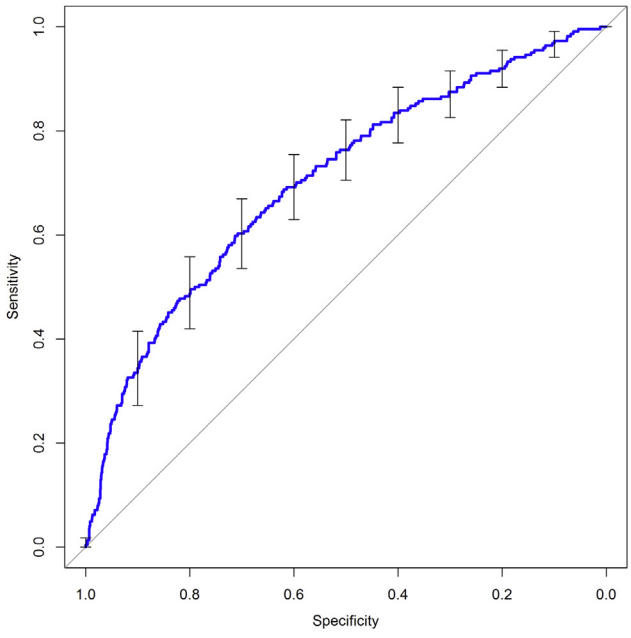


Fig. 3. Receiver-operating characteristic (ROC) curve for a logistic model predicting early adverse outcomes in the overall population. The ROC curve of the developed logistic model predicting (any) cycle 1 or 2 severe treatment-related toxicity is shown. The apparent area under the ROC curve (AUC) was 0.704 (95% confidence interval 0.666–0.743, optimism-corrected AUC 0.690).

When BSA was replaced by sex in the model for gastrointestinal toxicity, female sex was predictive of early onset toxicity (OR 1.71, 95% CI 1.12–2.61, $p = 0.0483$). Female sex was independently associated with dose reductions (of ≥20%), after adjusting for treatment regimen, BSA, renal function, and age (OR 2.05, 95% CI 1.33–3.16, $p = 0.0011$).

Of the other types of toxicity, haematological toxicity was related to renal function and DPD deficiency. None of the patient-related factors were associated with early severe HFS. The only factor associated with cardiac toxicity was female sex (OR 2.39, 95% CI 1.04–5.49, $p = 0.0405$).

The same predictors related to toxicity were related to hospitalisation for toxicity, except age. We investigated whether there were factors that increased risk of hospitalisation in addition to toxicity, by including maximum toxicity score in a model for hospitalisation along with candidate factors. None of the factors other than toxicity score showed an association with risk of hospitalisation. Age and BSA were associated with early discontinuation of treatment, but not in addition to toxicity score.

3.4. Higher risk of fatal treatment-related toxicity in the elderly and patients with elevated pre-treatment serum uracil concentrations

In view of the small number of events of fatal toxicity (n = 6), only univariable analyses were performed (Table 3). None of the treatment regimens was associated with fatal toxicity (details not shown). The distribution of fatal events was as follows: capecitabine plus platinum (three patients), capecitabine monotherapy (two patients), and capecitabine-based triplet combination (one patient).

Higher age was significantly associated with fatal treatment-related toxicity (Table 3 and Fig. S2). The median age of patients with fatal toxicity was 76 years (interquartile range 75–78, range 66–80). High pre-treatment uracil was also strongly associated with fatal toxicity (Table 3 and Fig. S2).

3.5. Discriminative ability of models predicting early onset toxicity

Fig. 3 shows the ROC curve for the model predicting global early severe toxicity, with treatment regimen, renal function, BSA, age, and *DPYD* polymorphisms as covariables. The apparent AUC was 0.704 (95% CI 0.666–0.743, optimism-corrected AUC 0.690).

4. Discussion

We investigated the impact of patient- and treatment-related factors as predictors of early onset severe

treatment-related toxicity in patients treated with capecitabine-based regimens in daily clinical care. In addition to DPD deficiency, renal function, BSA, and age contributed to patients' risk of experiencing early severe toxicity. Effect sizes of the individual patient-related factors were small to medium. However, the combined effect of patient-related factors resulted in large differences in risk of toxicity, and these differences may be clinically relevant for individual patients. For example, while the risk of early toxicity for a 40-year-old male with BSA 1.90 and eGFR 120 ml/min/1.73 m^2 treated with capecitabine plus platinum is predicted to be 7%, an 80-year-old female with BSA 1.60 and eGFR 60 ml/min/1.73 m^2 would be at 31% risk. When treated with a triplet combination, the risks would be 22% and 61%, respectively. Our results suggest that the order of strength of the individual predictors is DPD deficiency > renal function > BSA > age.

The observed effect of renal function is not unexpected, as creatinine clearance has been found to inversely correlate with risk of toxicity [14,15]. For this reason, a dose reduction of 25% is recommended in patients with an eGFR of 30–50 ml/min/1.73 m^2, and capecitabine is contraindicated in patients with an eGFR <30 ml/min/1.73 m^2 [16]. The mechanism by which renal function affects toxicity risk is not clear, and the dosing recommendations are established empirically based on an observed increased toxicity risk in patients with renal impairment [14,15]. Our population included almost exclusively patients with renal function >50 ml/min/1.73 m^2 (>99% of the patients), suggesting that even in patients without moderate or severe renal impairment, there is a clinically relevant effect of renal function on toxicity risk.

One study showed that exposure to 5′-DFUR – a metabolite of capecitabine and the direct precursor to 5-FU – was increased in patients with renal impairment, which correlated with increased risk of severe toxicity [15]. However, population PK analysis of phase III trials did not reveal a significant effect of calculated creatinine clearance (Cockcroft–Gault) on the pharmacokinetics of 5'-deoxy-5-fluorouridine (5'-DFUR) nor of capecitabine, 5'-deoxy-5-fluorocytidine (5'-DFCR), or 5-FU [17]. In addition, 5′-DFUR is cleared renally for only 10–15%, questioning whether there is a relevant effect of renal function on 5′-DFUR exposure in relation to toxicity risk [18]. Although the mechanism by which lowered renal function increases risk of toxicity remains unknown, renal function appears to be an important determinant of patients' risk of severe toxicity and patients with a GFR close to 50 ml/min should be treated with caution.

Age and BSA were associated with toxicity, consistent with the previous studies showing higher clearance of 5′-DFUR and 5-FU in patients with higher BSA, and reduced incidence of toxicity [19–22]. Our findings indicate that BSA-based dosing of capecitabine is justified and that dose capping in patients with higher BSA should be discouraged. In the previous studies, sex was found to be associated with toxicity and pharmacokinetics of capecitabine and 5-FU [8,23]. We found that differences in risk of toxicity were only apparent when not correcting for BSA, suggesting that body composition might explain the effect previously observed for sex [7]. However, we did find some evidence for an effect of sex, as dose reductions were more frequent in women, independent of BSA.

Despite lack of a significant association between age and global severe toxicity, age appeared to have a clinically relevant effect size. Age was significantly associated with gastrointestinal toxicity and, importantly, with fatal toxicity. Although patients with fatal toxicity were generally older patients, it should be mentioned that two out of three patients with fatal toxicity of whom pre-treatment uracil levels were available had extremely high uracil concentrations, indicative of DPD deficiency. This, and the fact that most other older patients could be treated safely, demonstrates that age by itself might not be a strong risk factor, but could be a relevant contributor to risk of fatal toxicity in the presence of other risk factors. Of note, it has previously been reported that a dose of capecitabine of 1250 mg/m^2 is not safe in the elderly, and 1000 mg/m^2 should therefore be considered standard for elderly patients [24].

As expected, type of treatment regimen was strongly associated with risk of toxicity. We did not formally aim to compare the safety profile of treatments with that in the respective pivotal studies, but incidences of early severe toxicity, of 10–40%, were in the same range as previously reported [1,3]. The incidence of fatal treatment-related toxicity, 0.4% in this study, was also in the same range as described previously [4].

The *DPYD* polymorphisms c.2846A>T and c.1679T>G are now established risk factors for toxicity, and our findings support the recommendation of reducing the starting dose in patients carrying either of these mutations [25]. We previously showed that elevated pre-treatment uracil concentration is a promising phenotypic marker of DPD deficiency which is potentially more sensitive to identify patients at risk of toxicity than *DPYD* polymorphisms, and the findings from this analysis further confirm this (submitted manuscript).

Strengths of our analysis are the large number of patients included, from multiple centers and with a wide spread of covariables. Our results reflect the routine, daily care situation, and the combined analysis of different treatment regimens provides insight into the relative risks associated with patient- and treatment-related factors in a typical oncology population. A limitation of our analysis is that we did not externally validate the identified predictors and their effect sizes. Our findings regarding the identified predictors are, however, consistent with the previous reports investigating 5-FU-associated toxicity.

5. Conclusion

This analysis shows that in a daily care population, renal function, body composition, and age, in addition to DPD deficiency, are associated with patients' risk of early onset severe capecitabine-associated toxicity. The presence of multiple risk factors may predispose patients to high risks of early severe toxicity, and these factors might be relevant to consider in evaluating the benefit–risk balance of treatment for individual patients.

Our study suggests that there is room for personalisation of treatment with fluoropyrimidines. A dosing algorithm, such as used in dosing of coumarin anticoagulants, could be valuable in dosing of fluoropyrimidines. This algorithm could include age and/or renal function in addition to BSA, as well as the patient's status regarding DPD pro-/deficiency. For patients with multiple risk factors, such as older patients with low renal function, an initially reduced dose and subsequent dose titration based on tolerance might be required to avoid severe and potentially lethal early toxicity.

Conflict of interest statement

The authors have declared no conflicts of interest.

Funding

No specific funding was used to support this analysis.

Acknowledgements

We gratefully thank all patients who participated in study NCT00838370.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2015.10.013.

References

[1] Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 2001;19:2282–92.

[2] Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19:4097–106.

[3] O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub J-P, Cervantes G, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002;20:2812–23.

[4] Mikhail SE, Sun JF, Marshall JL. Safety of capecitabine: a review. Expert Opin Drug Saf 2010;9:831–41. http://dx.doi.org/10.1517/14740338.2010.511610.

[5] Delea TE, Vera-Llonch M, Edelsberg JS, McGarry L, Anton S, Ulcickas-Yood M, et al. The incidence and cost of hospitalization for 5-FU toxicity among medicare beneficiaries with metastatic colorectal cancer. Value Health 2002;5:35–43. http://dx.doi.org/10.1046/j.1524-4733.2002.51083.x.

[6] Van Kuilenburg ABP. Dihydropyrimidine dehydrogenase and the efficacy and toxicity of 5-fluorouracil. Eur J Cancer 2004;40:939–50. http://dx.doi.org/10.1016/j.ejca.2003.12.004.

[7] Prado CMM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin Cancer Res 2007;13:3264–8. http://dx.doi.org/10.1158/1078-0432.CCR-06-3067.

[8] Stein BN, Petrelli NJ, Douglass HO, Driscoll DL, Arcangeli G, Meropol NJ. Age and sex are independent predictors of 5-fluorouracil toxicity. Analysis of a large scale phase III trial. Cancer 1995;75:11–7.

[9] Deenen MJ, Meulendijks D, Cats A, Sechterberger MK, Severens JL, Boot H, et al. Upfront Genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. J Clin Oncol 2015 Nov 16. pii: JCO.2015.63.1325. [Epub ahead of print].

[10] Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet 2005;44:1051–65. http://dx.doi.org/10.2165/00003088-200544100-00004.

[11] Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the modification of diet in renal disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;53:766–72. http://dx.doi.org/10.1373/clinchem.2006.077180.

[12] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.

[13] R v.3.1.1. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2014.

[14] Cassidy J. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 2002;13:566–75.

[15] Poole C, Gardiner J, Twelves C, Johnston P, Harper P, Cassidy J, et al. Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients. Cancer Chemother Pharmacol 2002;49:225–34. http://dx.doi.org/10.1007/s00280-001-0408-0.

[16] Scientific Discussion Capecitabine. European Medicines Agency (EMA); 2005. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000316/WC500058145.pdf [accessed 12.11.14].

[17] Gieschke R, Burger H-U, Reigner B, Blesch KS, Steimer J-L. Population pharmacokinetics and concentration-effect relationships of capecitabine metabolites in colorectal cancer patients. Br J Clin Pharmacol 2003;55:252–63.

[18] Reece PA, Olver IN, Morris RG, Bishop JF, Guentert TW, Hill HS, et al. Pharmacokinetic study of doxifluridine given by 5-day stepped-dose infusion. Cancer Chemother Pharmacol 1990;25:274–8.

[19] Gieschke R, Reigner B, Blesch KS, Steimer JL. Population pharmacokinetic analysis of the major metabolites of capecitabine. J Pharmacokinet Pharmacodyn 2002;29:25–47.

[20] Gusella M, Toso S, Ferrazzi E, Ferrari M, Padrini R. Relationships between body composition parameters and fluorouracil pharmacokinetics. Br J Clin Pharmacol 2002;54:131–9.

[21] Cassidy J, Twelves C, Cameron D. Bioequivalence of two tablet formulations of capecitabine and exploration of age, gender, body surface area, and creatinine clearance as factors influencing systemic. Cancer Chemother Pharmacol 1999:453–60.

[22] Meyerhardt JA, Tepper JE, Niedzwiecki D, Hollis DR, McCollum AD, Brady D, et al. Impact of body mass index on outcomes and treatment-related toxicity in patients with stage II and III rectal cancer: findings from intergroup trial 0114. J Clin Oncol 2004;22:648–57. http://dx.doi.org/10.1200/JCO.2004.07.121.

[23] Gusella M, Crepaldi G, Barile C, Bononi a, Menon D, Toso S, et al. Pharmacokinetic and demographic markers of 5-fluorouracil toxicity in 181 patients on adjuvant therapy for colorectal cancer. Ann Oncol 2006;17:1656–60. http://dx.doi.org/10.1093/annonc/mdl284.

[24] Bajetta E, Procopio G, Celio L, Gattinoni L, Della Torre S, Mariani L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 2005;23:2155–61. http://dx.doi.org/10.1200/JCO.2005.02.167.

[25] Caudle KE, Thorn CF, Klein TE, Swen JJ, McLeod HL, Diasio RB, et al. Clinical pharmacogenetics implementation consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Clin Pharmacol Ther 2013;94:640–5. http://dx.doi.org/10.1038/clpt.2013.172.