Fluoropyrimidine dose individualization based on pretreatment uracil levels: safety and pharmacokinetic analysis from the Alpe2U study

M. de With[1*], J. Knikman[2*], A. Baars[3], G.-J. Creemers[4], H.J. Droogendijk[5], W.E. Fiets[6], A.L.T. Imholz[7], L..B.J. Valkenburg-van Iersel[8], F.J.F. Jeurissen[9], C.M.P.W. Mandigers[10], R.H.N. van Schaik[11], B.J.C. van den Bosch[12], H. Rosing[13], J.H. Beijnen[13,14], J.J. Swen[15] , H. Gelderblom[16], J.H.M. Schellens[17], R.H.J. Mathijssen[18], H.-J. Guchelaar[19], A. Cats[20]

1] Dept. of Medical Oncology and Clinical Chemistry, Erasmus MC Cancer Institute, Rotterdam, The Netherlands.
2] Div. of Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
3] Dept. of Medical Oncology, Hospital Gelderse Vallei, Ede, The Netherlands.
4] Dept. of Medical Oncology, Catharina Hospital, Eindhoven, The Netherlands,
5] Dept. of Internal Medicine, Bravis Hospital, Roosendaal, The Netherlands.
6] Dept. of Internal Medicine, Medical Center Leeuwarden, Leeuwarden, The Netherlands.
7] Dept. of Medical Oncology, Deventer hospital, Deventer, The Netherlands.
8] Dept. of Medical Oncology, Maastricht University Medical Center, Maastricht, The Netherlands.
9] Dept. of Internal Medicine, Haaglanden Medical Center, The Hague, The Netherlands.
10] Dept. of Internal Medicine, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands.
11] Dept. of Clinical Chemistry, Erasmus Medical Center, Rotterdam, The Netherlands.
12] Dept. of Clinical Genetics, Maastricht University Medical Center, Maastricht, The Netherlands.
13] Dept. of Pharmacy and Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
14] Dev. of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands.
15] Dept. of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands.
16] Dept. of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands.
17] Science Faculty, Utrecht University, Utrecht, The Netherlands.
18] Dept. of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands.
19] Dept. of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands.
20] Dept. of Gastrointestinal Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
*Authors contributed equally.

INTRODUCTION

- Risk of fluoropyrimidine-related adverse events (AEs) can be significantly reduced through dose reduction in DPD deficient patients, however still 23% of wild type patients develop severe AEs[1]
- DPD is the main metabolizing enzyme of fluoropyrimidines
- In 2020 EMA stated that screening on DPD deficiency should be performed before fluoropyrimidine treatment by:
  1] *DPYD* genotyping, or
  2] DPD phenotyping by using plasma uracil (U) levels[2]
- Based on previous studies, patients with U > 16 ng/ml are considered DPD deficient[3]

PRIMARY OBJECTIVE

The Alpe2U study (NCT04194957) is the first prospective multicenter study investigating if severe fluoropyrimidine-related AEs could be reduced by a fluoropyrimidine dose individualization based on combined *DPYD* genotype and U levels.

METHODS

- Results of a planned interim-analysis in 654 enrolled patients from 14 Dutch hospitals are presented
- Prior to fluoropyrimidine-based treatment, the following was done:
  1) genotyping for *DPYD**2A, 2846A>T, 1679T>G and 1236G>A
  2) measuring U levels in fasting state, between 8-10h AM
  3) measuring DPD enzyme activity in peripheral blood mononuclear cells (PBMCs)
- Heterozygous variant carriers and *DPYD* wild types with U > 16 ng/ml received a 50% dose reduction followed by dose titration based on clinical judgement
- Pharmacokinetic sampling of *DPYD* wild types with U > 16 ng/ml was done in the first treatment cycle and compared with a reference cohort of 22 wild types receiving full dose[4]
- AEs during fluoropyrimidine-treatment were collected
- Uracil levels and DPD enzyme activity in PBMCs were compared

RESULTS

Baseline patients' characteristics
***DPYD* wild types with uracil > 16 ng/ml**

Characteristics	50% dose n = 23 patients
Sex (%)	
Male	9 (39.1)
Age (years, median, [IQR])	62.0 [55.5-70.5]
ECOG performance status (%)	
0	6 (27.3)
1	13 (59.1)
2	3 (13.6)
BSA (median, [IQR])	1.91 [1.80-2.05]
Primary tumor type (%)	
Breast	6 (26.1)
Colorectal	11 (47.8)
Esophageal	4 (17.4)
Gastric	1 (4.3)
Bladder	1 (4.3)
Cancer stage (%)	
Local	1 (4.3)
Locally advanced	6 (26.1)
Metastatic	16 (69.6)
Treatment regimen (%)	
5-fluorouracil + oxaliplatin	1 (4.3)
Capecitabine monotherapy	5 (21.8)
Capecitabine monotherapy + radiotherapy	3 (13.0)
Capecitabine + oxaliplatin	8 (34.8)
Capecitabine + oxaliplatin + bevacizumab	2 (8.7)
Capecitabine + oxaliplatin + trastuzumab	1 (4.3)
Capecitabine + trastuzumab	1 (4.3)
Capecitabine + anastrozole	2 (8.7)

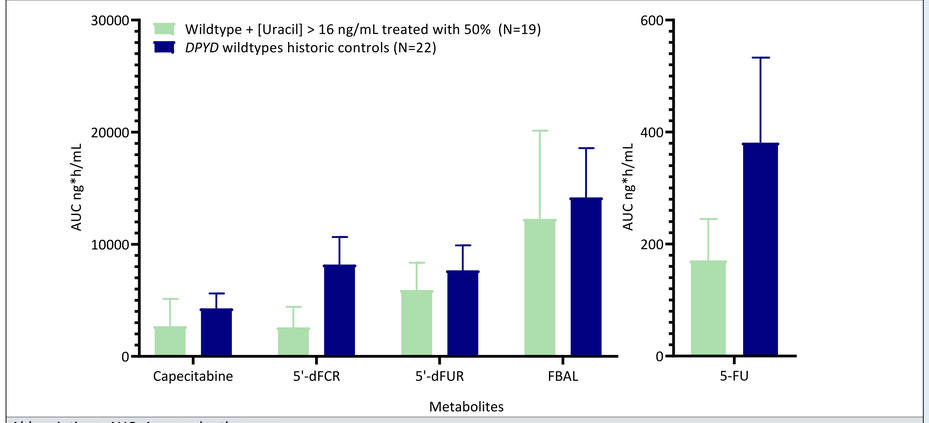
Abbreviations: IQR: interquartile range.

DPD deficiency tests and fluoropyrimidine treatment outcome
***DPYD* wild types with uracil > 16 ng/ml**

Characteristics	50% dose n = 23 patients
DPD deficiency tests (median, [IQR])	
Uracil	18.40 [17.45-22.60]
Dihydrouracil	151.00 [129.75-163.75]
Uracil/Dihydrouracil – ratio	7.43 [6.36-8.04]
DPD enzyme activity	11.00 [7.60-14.30]
Dose intensity (median % of standard dose, [IQR])	
First cycle	50.0 [50.0-50.3]
All cycles	50.2 [50.0-62.4]
Occurrence of fluoropyrimidine-related AEs (%)*	
CTCAE grade 0	10 (43.3)
CTCAE grade 1	2 (8.7)
CTCAE grade 2	6 (26.1)
CTCAE grade 3	5 (21.7)

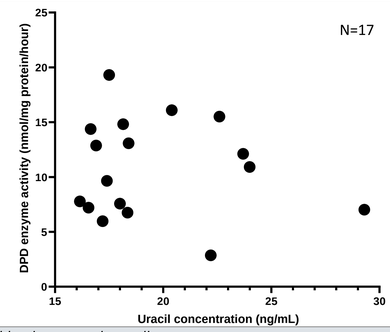
** Highest grade during fluoropyrimidine treatment. Preliminary results.*
Abbreviations: IQR: interquartile range; DPD: dihydropyrimidine dehydrogenase; AEs: adverse events; CTCAE: common terminology criteria for adverse events.

Pharmacokinetic data



Abbreviations: AUC: Area under the curve.

Correlation uracil levels and DPD enzyme activity in PBMCs



Abbreviations: PBMCs: peripheral blood mononuclear cells.

CONCLUSION

- Fluoropyrimidine dose individualization based on U levels may be accompanied with high risk of underdosing.
- Severe fluoropyrimidine-related toxicity could not be prevented by pretreatment uracil testing.
- The use of U levels alone for dose individualization of fluoropyrimidines should be reconsidered.

References
1] Henricks *et al.* Lancet Oncology, 2018.
2] European Medicines Agency, EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine, 2020.
3] Meulendijks *et al.*, British Journal of Cancer, 2017.
4] Deenen *et al.*, Cancer Chemotherapy and Pharmacology, 2015.

Poster ESMO Congress 2022 70P

Mirjam de With
m.dewith@erasmusmc.nl
0031 10 70 407 99

M. de With has no conflicts of interest