Recommendation on testing for dihydropyrimidine dehydrogenase deficiency in the ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

Deenen, M.J.; Meulendijks, D.

Recommendation on testing for dihydropyrimidine dehydrogenase deficiency in the ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

ESMO Clinical Practice Guidelines are an important guidance for health care providers in oncology and their patients by providing evidence-based clinical practice recommendations. Therefore, the authors of the 2016 'ESMO consensus guidelines for the management of patients with metastatic colorectal cancer' are to be appraised for their comprehensive work [1]. Because these guidelines greatly impact clinical practice, we respectfully raise one concern regarding the recommendation on testing for dihydropyrimidine dehydrogenase (DPD) deficiency:

> *'DPD testing before 5-FU administration remains an option but is not routinely recommended [II, D]'*

In our view, this recommendation does not adequately reflect the current evidence supporting the clinical utility of upfront screening for DPD deficiency. This is of great concern, as it affects the safety of approximately 20 000 DPD-deficient patients, i.e. 3–5% of the ∼450 000 patients diagnosed annually with colorectal cancer in Europe.

Fluoropyrimidine-associated toxicity occurs in ∼30% of the treated patients, with 0.5–1% suffering fatal treatment-related toxicity, and thereby, treatment-related toxicity has a substantial impact on patients' quality of life [2]. Studies over the past 30 years have yielded a vast amount of clinical evidence showing that DPD deficiency is strongly associated with severe and fatal fluoropyrimidine-induced toxicity [3]. DPD deficiency mainly results from deleterious polymorphisms in *DPYD*, the gene encoding DPD. Clinical validity of four *DPYD* variants as risk factors for fluoropyrimidine-associated toxicity has been robustly demonstrated in a recent meta-analysis including 7365 patients, i.e. *DPYD**2A (relative risk 2.9, $P < 0.0001$), c.2846A > T (relative risk 3.0, $P < 0.0001$) c.1679T > G (relative risk 4.4, $P < 0.0001$), and c.1236G > A/Haplotype B3 (relative risk 1.6, $P < 0.0001$) [4].

Most importantly, a recent large prospective study has demonstrated the clinical utility of upfront *DPYD* screening. A total of 1631 patients was prospectively screened for *DPYD**2A and treated with fluoropyrimidine-based chemotherapy. *DPYD**2A carriers were treated with a 50% reduced fluoropyrimidine starting dose [5]. *DPYD**2A-guided dosing proved to be feasible in routine clinical practice, and reduced the incidence of severe toxicity in *DPYD**2A carriers from 73% (in historical controls) to 28% ($P < 0.001$), while the incidence of fatal toxicity reduced from 10% to 0%. Importantly, the cost-analysis showed that *DPYD* genotype-guided dosing not only prevented toxicity, but was also net cost-saving (€45 per patient) [5]. Based on the demonstrated clinical validity of the additional three *DPYD* variants, screening for these variants will further increase net cost-savings by further prevention of fluoropyrimidine-induced severe toxicity and toxicity-associated hospitalizations.

We consider it in the best interest of patients to use the best available upfront screening methods in order to prevent DPD deficiency-associated severe and fatal toxicity. Current evidence supports upfront *DPYD* screening, followed by genotype-guided dosing, based on dosing recommendations by the Clinical Pharmacogenetics Implementation Consortium (CPIC; www.pharmgkb.org). We do acknowledge that screening for *DPYD* variants is not the panacea that is able to avoid all fluoropyrimidine-associated toxicities, as not all toxicities are DPD deficiency-associated. However, the evidence regarding clinical utility of *DPYD* genotype-guided dosing of fluoropyrimidines is such that it cannot be disregarded at this stage.

In conclusion, patient safety and clinical benefit can be increased substantially by *DPYD* genotype-guided dosing. Based on the available evidence, we strongly recommend to reconsider recommendation 7, taking into account all published data relevant to this issue.

M. J. Deenen[1,2*] & D. Meulendijks[3]

[1]Department of Clinical Pharmacy, Catharina Hospital, Eindhoven; [2]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden; [3]Dutch Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands

(*E-mail: maarten.deenen@catharinaziekenhuis.nl)

Funding

None declared.

Disclosure

The authors have declared no conflicts of interest. D.M. is affiliated to the Dutch Medicines Evaluation Board. The content of this letter, however, reflects the personal opinion of the author and do not necessarily reflect the views of the agency.

References

1. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016; 27: 1386–1422.
2. Mikhail SE, Sun JF, Marshall JL. Safety of capecitabine: a review. Expert Opin Drug Saf 2010; 9: 831–841.
3. van Kuilenburg ABP. Dihydropyrimidine dehydrogenase and the efficacy and toxicity of 5-fluorouracil. Eur J Cancer 2004; 40: 939–950.
4. Meulendijks D, Henricks LM, Sonke GS et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015; 16: 1639–1650.
5. Deenen MJ, Meulendijks D, Cats A et al. Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. J Clin Oncol 2016; 34: 227–234.

doi:10.1093/annonc/mdw533
Published online 3 October 2016