Medical information letter on DPD deficiency in response to a question for more information after the DHCP letter

Background DPD deficiency fluoropyrimidines and mandatory change to the product information

Parenteral 5-flurouracil and related substances such as capecitabine and tegafur are systemic fluoropyrimidines widely used in oncology as the backbone of a large percentage of current chemotherapy regimens across a broad spectrum of cancers. DPD is the main metabolising enzyme of 5-fluorouracil (80-85% of catabolic clearance) and its activity can widely vary between individuals. DPD deficiency can also be highly variable and is partly linked to genetic polymorphisms in its gene DPYD but may also have other causes. Prevalence of partial and complete DPD deficiency in the entire population varies between different sources and has been estimated with approximately 3%–9% and 0.01%–0.5%, respectively [1,2].

Treatment of patients with DPD deficiency with 5-fluorouracil or related substances can result in severe and life-threatening side effects such as severe diarrhea, stomatitis, neutropenia and neurotoxicity. DPD-deficiency related toxicity usually occurs during the first cycle of treatment [1,2]. Fluoropyrimidine-associated toxicity in DPD deficient patient seem to correlate with its reduced DPD activity. The European Medicines Agency is therefore of the view that in patients with known complete DPD deficiency, the benefit-risk balance of parenteral 5-fluorouracil and related substances capecitabine, tegafur and flucytosine is not favourable and should be contra-indicated.

The clinical situation in case of partial loss of DPD activity is less clear. Partial DPD deficiency is also associated with an increased risk for severe toxicity, but in the absence of suitable alternative treatment, patients should be treated with caution and a lower starting dose should be considered. Irrespective of being completely or partially DPD deficient, this implies that patients should be tested on DPD deficiency before treatment, which is an important change of current practice in relation to the prescription of 5-flurouracil and related substances.

Genotyping and phenotyping are to date considered to be the best available methods for identification of DPD deficient patients. Both methods have limitations and are therefore recommended to be used in parallel to identify DPD deficient patients. Genotyping is the easiest to perform, most robust and best implemented technique. However, genotyping can only identify DPD deficiencies associated with the tested DPYD variants and miss rare or unknown DPYD variants or non-genetic factors. Moreover, DPYD genotype and DPD activity only correlate moderately. DPD phenotyping may overcome these challenges by direct measurement of the endogenous DPD substrate uracil in blood. However, there are uncertainties on uracil cut-off levels defining complete and partial DPD deficiency, as these have not been validated prospectively. In addition, solid data on both safety and efficacy of adaptive fluoropyrimidine dosing following a test results of DPD phenotyping is missing.

In view of the above, the EMA concludes that the benefit-risk balance of 5-fluorouracil and related substances capecitabine, tegafur and flucytosine containing products remains favourable subject to amending the product information to include upfront DPD testing.

Teysuno® and DPD deficiency

The EMA recommendations are made for fluoropyrimidines as a group. Several studies have shown that complete DPD deficiency is related to severe toxicity of these compounds [1,2]. As with the other fluoropyrimidines, complete DPD deficiency has therefore always been mentioned as a contraindication in the SmPC of Teysuno®.

> Teysuno indication
>
> Teysuno® (S-1) is approved in adults for the treatment of advanced gastric cancer when given in combination with cisplatin. It is given orally at a dose of 25 mg/m^2 B.I.D. for 21 days of a 28-day cycle along with 75 mg/m^2 cisplatin administered by intravenous infusion once every 4 weeks. [3]

In patients with partial deficiency, the situation is different. It is important to emphasize here, that Teysuno® is significantly different from other fluoropyrimidines. First, for theoretical reasons, Teysuno® is likely to be less affected as compared to the other fluoropyrimidines as Teysuno® contains a strong DPD inhibitor, gimeracil, which inhibits DPD activity and contributes to a relatively gradual accumulation of 5-FU in all patients after administration of Teysuno® [4, 5].

Second, Teysuno® pharmacovigilance data in Europe show that since its introduction in 2011, no report of adverse event linked to DPD deficiency has been received. Upfront DPD testing was not done for patients in Europe. Taking the prevalence of partial DPD deficiency into account, several patients would have been expected to have had toxicities upon treatment with Teysuno®.

Third, Teysuno® is registered in 12 Asian countries as S-1 (MAH Taiho) for a variety of indications in solid tumours and over 2 million patients (> 99% of the prescriptions worldwide) have been treated in this region until December 2019. As of June 2020, safety measures on DPD testing prior to Teysuno® prescription have not been decided in Japan. As in Europe, the initial dose level is recommended to be selected based on body surface area (BSA) and dose adaption should be made according to CrCl level. When it is known that a patient is completely DPD deficient, Teysuno® is contraindicated as everywhere else.

Recommendations for using Teysuno® in patients with partial DPD deficiency

Whilst there is no evidence showing that partial DPD deficiency is associated with significant toxicity, an increased risk with Teysuno® in patients with partial DPD deficiency cannot be completely excluded. In agreement with EMA recommendations and for patients where there is no suitable alternative treatment, we therefore recommend that patients are treated with Teysuno® with caution. A reduced starting dose should be considered to limit the chances of toxicity, although this may impact the initial efficacy of the treatment. Specifically, we recommend using the dose reduction schedule as described in the SmPC. Depending on the patient therefore, the starting dose could be reduced by one step to 20mg/m^2 or two steps to 15 mg/m^2, reducing the dose with 25% to 50% respectively. In the absence of serious toxicity, subsequent doses may be increased stepwise to normal with careful monitoring

Summary in bullets:

Background DPD deficiency:

- Fluoropyrimidines are widely used as the backbone in chemotherapy regimens
- Fluoropyrimidines are primarily degraded by DPD
- Prevalence of partial and complete DPD deficiency is 3%–9% and 0.01%–0.3%, respectively
- Treatment of patients with DPD deficiency with fluoropyrimidines can result in severe and life-threatening side effects:
    - Treatment is contra-indicated in patients with known complete DPD deficiency
    - Severe toxicity cannot be excluded in patients with partial DPD deficiency
- Before fluoropyrimidines are administered, presence of DPD deficiency should be tested by:
    - Genotyping
      and
    - Phenotyping
- Benefit-risk balance of fluoropyrimidines remains favourable, with upfront DPD testing implemented

Teysuno® and DPD

- Teysuno® contains a fluoropyrimidine and is thus contra-indicated in patients with known complete DPD deficiency
- Teysuno® is different from all other fluoropyrimidines, as it contains a strong DPD inhibitor
- In patients treated with Teysuno®:
    - Teysuno® is less likely to be toxic in patients with partial DPD deficiency compared to other fluoropyrimidines as it contains a strong DPD inhibitor (gimeracil)
    - Retrospective European pharmacovigilance data since its introduction in 2011 highlights that no report of adverse event linked to DPD deficiency has been received
- Severe toxicity with Teysuno® cannot be fully excluded in patients with partial DPD deficiency

Recommendations for Teysuno® in case of partial DPD deficiency

- When patients need treatment and are partially DPD deficient, Teysuno® is recommended to be started at a lower starting dose, which can be escalated with careful monitoring in the absence of serious toxicity
- Suspected adverse reactions should always be reported via the national reporting system.

References

1. Mattison LK, Fourie J, Desmond RA, Modak A, Saif MW, Diasio RB. Increased prevalence of dihydropyrimidine dehydrogenase deficiency in African Americans compared with Caucasians. Clin Cancer Res 2006; 12: 5491–95.
2. Johnson MR, Diasio RB. Importance of dihydropyrimidine dehydrogenase (DPD) deficiency in patients exhibiting toxicity following treatment with 5-fluorouracil. Adv Enzyme Regul 2001; 41: 151–57.
3. Teysuno SmPC
4. Milano G1. Fluoropyrimidines and DPD testing: is there truly an inexorable link? Eur J Cancer. 2019 May; 113:45-46.
5. Zhu, AX, et al. Phase I and pharmacokinetic study of S-1 administered for 14 days in a 21-day cycle in patients with advanced upper gastrointestinal cancer. Cancer Chemother Pharmacol, 2007, 59:285–293.