Case Report

Safety Report of TAS-102 in a Patient With Reduced DPD Activity

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Clinical Practice Points

- Trifluridine/tipiriracil (TAS-102, Lonsurf) is a novel oral fluoropyrimidine. In literature, no data are available regarding the use of TAS-102 in patients with reduced DPD activity.
- We describe the first report of safety administration of TAS-102 in a DPD-deficient patient.
- Our case suggests the possibility of administering TAS-102 to patients with DPD deficiencies.

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Introduction

Fluoropyrimidines (5-fluorouracil [5-FU] and its prodrug capecitabine) are widely used alone or in combination with other chemotherapy, and they are the backbone treatment for many solid tumors. The use of these drugs might be associated with severe gastrointestinal and hematologic grade 3 to 4 toxicities.[1]

About 80% of 5-FU is inactivated by 5-fluoro-dihydrouracil (5-FDHU) by dihydropyrimidine dehydrogenase (DPD), the main enzyme of fluoropyrimidine metabolism. Polymorphisms in the coding region of the dihydropyrimidine dehydrogenase gene (DPYD) cause reduced enzymatic activity of DPD and may result in the development of serious grade 3 to 4 toxicity after a standard dose of the drug (gastrointestinal, medullary, and hand-foot syndrome).[2]

Trifluridine/tipiriracil (TAS-102, Lonsurf) is a novel anti-tumoral agent combining trifluridine (antineoplastic thymidine-based nucleoside analogue) with tipiracil hydrochroride (thymidine phosphorylase inhibitor) and is a treatment approved for patients with metastatic colorectal cancer refractory or intolerant to standard treatment.[3]

In literature, no data are available regarding the use of TAS-102 in patients with reduced DPD activity.

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Case Report

In April 2017, a 77-year-old woman underwent an emergency Miles abdomino-perineal resection for a bleeding lesion of the rectum. The final histologic diagnosis was: adenocarcinoma G3 pT3pN2 (4/13) M1 (multiple liver lesions) KRAS-mutated (exon 2, codon 12, c35G>A), NRAS wild-type, BRAF wild-type. Her past medical history included hypertension and atrial fibrillation, and the patient was on anticoagulant therapy.

Considering the histologic result and the stage, after the cardiologist's consult, first-line chemotherapy with FOLFOX4 (oxaliplatin 85 mg/mq day 1 every 14 days [q14]; 5-FU 400 mg/mq days 1,2 [q14], 5-FU 1200 mg/mq ic 48 hours [q14] and leucovorin 100 mg/mq days 1,2 [q14]) was started. Computed tomography (CT) scans after 6 cycles of chemotherapy (October 2017) showed partial response on liver metastasis. After the ninth cycle of FOLFOX (December 2017), she developed severe diarrhea (grade 3) that required admission to the hospital. We performed a stool culture (with all negative results) and a genetic analysis for DPYD allelic variants. Our laboratory performed allelic discrimination assay using real-time polymerase chain reaction. The analyzed allelic variants of the DPYD gene were: DPYD*2A (IVS14-1G>A, c.1905+1G>A, rs3918290), DPYD*13 (p.I560S, c.1679T>G, rs55886062), DPYD D949V (p.D949V, c.2846A>T, rs67376798), and DPYD IVS10 (c.1129-5923C>G, rs75017182). DPYD IVS10 was found in heterozygosity in our patient. Considering this result, FOLFOX chemotherapy was suspended, and chemotherapy with weekly irinotecan (125 mg every 7 days) was started; she received 4 doses of irinotecan, but it was suspended for persistent gastrointestinal toxicity. CT scans performed in May 2018 showed partial response on the liver metastasis. Considering the previous oncologic treatment, partial positivity of DPD, and the patient's willingness to being treated, a third-line chemotherapy with TAS-102, with reduced dosage for development of renal insufficiency

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(30 mg/mq twice daily, days 1-5 and days 8-12 every 28 days), was started. The patients received 5 cycles of TAS-102 (June-December 2018). The treatment was well-tolerated, and the patient did not experience medullary or gastrointestinal toxicity. CT scans after 3 cycles (October 2018) showed partial response. She died of sepsis in January 2019.

To the best of our knowledge, this is the first case report of a DPD allelic heterozygous variant carrier treated with TAS-102.

To note, our patient was pretreated with oxaliplatin, 5-FU, and irinotecan, and she experienced severe gastrointestinal toxicity with all of the treatments that required admission to the hospital. On the contrary, treatment with TAS-102 was safe and effective.

Discussion

TAS-102 is a treatment option in third-line therapy for metastatic colorectal cancer. TAS-102 is a novel oral fluoropyrimidine and, compared with the other fluoropyrimidines (5-FU and capecitabine), has a completely different mechanism of action. In addition to inhibition of thymidylate synthase (the mechanism of action of classical fluoropyrimidines), TAS-102's major mechanism of action is incorporation into DNA, thereby causing DNA damage.[4]

Previous pharmacogenetic studies have shown the prognostic impact of DPYD gene polymorphism on 5−FU-related toxicity.

The DPYD gene is composed of 23 exons, and more than 30 polymorphisms between exonic and intronic DPYD are reported in the literature. The most frequent mutation is IVS14 + 1G>A, which shows the substitution of the first base, a guanine (G), at the end of exon 14, with an adenine (A). The mutation does not allow recognition of the splicing site in the GT sequence at the 5' end of intron 14, causing deletion of the entire exon preceding the mutation, resulting in a loss of 165 pair of bases, generating an incomplete protein with no enzymatic activity. Patients carrying the mutation in IVS14 + 1GA heterozygosis need a reduction of treatment of at least 50%, and carriers of the homozygous mutant IVS14 + AA genotype should not be treated with fluoropyrimidine because all the subjects carrying the mutation in homozygosis are risking lethal gastrointestinal and hematologic toxicities.[5]

The most frequent mutation is IVS14 + 1G>A, but other mutations of the DPYD gene have been described in the literature; not all of them are associated with an enzymatic deficiency.

Molecular analysis performed in our laboratory highlighted the presence of DPYD IVS10 in heterozygosity. The intronic variant IVS10, rs75017182, of the DPYD gene has recently emerged as a possible predictor of 5-FU toxicity. According to a Mayo Clinic study, the heterozygous carriers of this variant have reduced the enzymatic activity of DPD (about 35%),[6] and this result possibly explains the gastrointestinal toxicity after FOLFOX chemotherapy.

In a large prospective recent study, Henricks et al[7] showed that DPYD genotyping is feasible in routine clinical practice and that the safety of patients was improved by dose individualization of fluoropyrimidines on the basis of the DPYD genotype. Dose reduction of 50% in heterozygous DPYD*2A and c.1679T>G carriers markedly reduced toxicity risk. Applied dose reductions of 25% in heterozygous c.1236G>A and c.2846A>T carriers were instead insufficient to lower the risk of fluoropyrimidine-related toxicity to the observed risk in wild-type patients. The authors conclude that a larger initial dose reduction of 50% for c.2846A>T and c.1236G>A carriers, with subsequent individual dose titrations, could be considered.

DPD deficiency is generally not assessed in routine clinical practice before 5-FU administration. Recent evidences suggest considering DPYD pharmacogenetics in the pre-treatment phase for the safety of patients undergoing fluoropyrimidine-based chemotherapy,[8,9] particularly in the adjuvant setting. DPYD pharmacogenetics is also recommended during treatment in the metastatic setting in case of gastrointestinal toxicity grade > 3, hematologic toxicity grade 4, or in cases of unexpected toxicity.[10]

TAS-102 follows an alternative activation pathway via thymidine kinase and is not a substrate for DPD.[4] Trifluridine is primarily eliminated via TPase metabolism to form an inactive metabolite, FTY. Trifluridine is absorbed and excreted in the urine as FTY and isomers trifluridine-glucuronide.

This different mechanism of action also explains the different cardiotoxic profile of TAS-102 compared with the other fluoropyrimidines.[11] The fact that TAS-102 is not catabolized by DPD[12] suggests a safe use of the drug in DPD-deficient patients.

To the best of our knowledge, very few reports are available regarding the safe use of raltitrexed, which represents another option in this setting.[13,14]

Conclusion

We describe the first report of administration of TAS-102 in a DPD-deficient patient.

Our case and the available literature suggest the possibility of safely administering TAS-102 in DPD-deficient patients.

Disclosure

The authors have stated that they have no conflicts of interest.

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