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Educating the Healthcare Community About Safe Medication Practices

Screening for dihydropyrimidine dehydrogenase (DPD) deficiency in fluorouracil patients: Why not?

ISMP is aware of several reports of patients who suffered severe toxicities or even death from the fluoropyrimidine chemotherapy drugs, fluorouracil and capecitabine (**XELODA**), an oral prodrug that is metabolized to fluorouracil after ingestion. These patients had a genetic condition called dihydropyrimidine dehydrogenase (DPD) deficiency, a diagnosis that neither the patients nor their doctors were aware of until it was too late. The DPD enzyme is critical for the metabolism of fluoropyrimidine drugs. With deficient enzyme function, patients can experience severe toxicities with standard doses of fluoropyrimidine chemotherapy.[1] While the incidence of DPD deficiency is relatively low, ranging from 1 to 7 percent of the population depending on ancestry,[2] the consequences are potentially fatal.

Recent Event

A recently reported case involved a patient with breast cancer who was prescribed capecitabine. Within the first week of treatment, she began to develop mild drug-related symptoms including fatigue, weight loss, loss of appetite, and diarrhea. By the second week, her symptoms worsened, including mucositis, hand-foot syndrome (skin reaction caused by leakage of the chemotherapy through capillaries in the palms of the hands and soles of the feet), extreme weight loss, fatigue, diarrhea, and a cough. After completing her first 2 weeks of therapy, she had become so weak that she required hospitalization. After hospitalization, her symptoms continued to worsen, including hand and foot desquamation, severe mucositis, dry eyes requiring artificial tears, delirium, and prolonged leukopenia. Her mouth, lips, throat, and esophagus were covered with lesions and blood. Her hair was falling out. Eventually she became unresponsive. Only later was it found that she had a DPD deficiency, which decreased her body's ability to clear the fluorouracil. She died just one month after starting therapy.

ISMP was heartbroken to learn about this preventable death, as a DPD deficiency can be detected through genetic testing prior to starting fluoropyrimidine chemotherapy. Having this information beforehand allows providers to preemptively reduce the dose of the patient's therapy and mitigate potential toxicities, or not give therapy at all if the patient is totally deficient, as no fluorouracil dose has been proven safe for patients with complete absence of DPD activity.

Screening for DPD Deficiency in Other Countries

Recently, the European Medicines Agency (EMA), the French regulatory agency (L'Agence nationale de sécurité du médicament et des produits de santé [ANSM]), and the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom, have all provided guidelines for preemptive DPD testing for patients scheduled to receive fluoropyrimidine chemotherapy.[3] But in the US, the National Comprehensive Cancer Network (NCCN) has not recommended universal pretreatment DPD deficiency screening,[4] and it is not currently the standard of care despite the known risks. Patient advocates have filed citizen petitions with the US Food and Drug Administration (FDA)[5] requesting a Boxed Warning in product labeling to reflect the need for patient screening. FDA-approved labeling for fluorouracil and capecitabine discusses

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SAFETY brief

Improved safety needed for pediatric pegfilgrastim use. ISMP has received error reports involving pediatric patients who are receiving injectable medications as outpatients and require the removal of "partial doses" from a prefilled syringe. For example, Amgen's **NEULASTA** (pegfilgrastim), which is used primarily for the prevention of chemotherapy-induced neutropenia, is only available in a 6 mg prefilled syringe, the intended dose for adults. The same is true for biosimilar versions, **FULPHILA** (pegfilgrastim-jmdb), **UDENYCA** (pegfilgrastim-cbqv), **ZIEXTENZO** (pegfilgrastim-bmez) (**Figure 1**), and **NYVEPRIA** (pegfilgrastim-apgf). Yet the package insert includes a table for dosing pediatric patients under 45 kg that includes volumes less than 0.6 mL (6 mg). Furthermore, despite the weight-based pediatric dosing, confoundedly, the product labeling also states, "Note: The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation

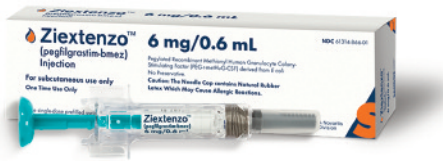

Figure 1. Pegfilgrastim-bmez (6 mg/0.6 mL) biosimilar syringe has no graduated markings.

marks, which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors."

The error reports we have seen indicate that parents are sometimes instructed to withdraw a partial dose from the prefilled syringe using an empty sterile syringe and needle. While this is certainly not a risk-

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DPD deficiency and the risk to patients, noting that patients with partial DPD activity may have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil. So far, nothing in US product labeling recommends (or requires) screening patients for DPD deficiency prior to initiating fluoropyrimidine chemotherapy.

Pros and Cons of Screening for DPD Deficiency

If the technology exists to detect the deficiency through genotyping, and the consequences of not doing so in advance of therapy with a fluoropyrimidine drug potentially may lead to patient harm and death, why wouldn't providers preemptively screen patients? Several concerns have been raised regarding universal pretreatment screening.

Cost of screening. Insurance companies may not cover the cost of DPD genetic testing, citing the test to be investigational.[6] However, analyses of cost effectiveness show that screening prior to therapy, combined with preemptive dose reductions, is a cost-effective option compared to no screening, given the severe toxicity-related hospitalization of patients who have a DPD deficiency and receive full-dose fluorouracil or capecitabine.[7,8]

Potential delay in care. Providers have expressed concern that preemptive screening for all patients scheduled to receive fluoropyrimidine chemotherapy may cause a delay in treatment.[6] However, based on other discussions, it appears that the genetic testing can be completed in a reasonable amount of time. According to laboratory personnel who we spoke with, in-house testing results can be available in 2 to 3 days, and external laboratory testing results can be available in 3 to 10 days. In most (but not all) cases, waiting for the genetic testing results is reasonable as workup and decisions are being made regarding cancer treatment. Or, at least screening can take place concurrently with therapy initiation since coordinating the start of therapy may take a few days.

Potential lack of consensus on dosing. Some clinicians have also cited a lack of consensus on preemptive dose reductions for DPD deficiency to be a barrier to widespread testing. However, clear guidance is available from the Clinical Pharmacogenetics Implementation Consortium (CPIC), a leading authority on implementing pharmacogenetic testing for patient care.[2,3] Their dosing recommendations address the varying degrees of DPD deficiency for safe and effective use of fluoropyrimidines in all patients.[2]

Potential decreased efficacy against cancer. Another concern raised is the uncertainty and potential negative impact on treatment efficacy if preemptive testing leads to a dose reduction. However, pharmacokinetic studies show that patients with DPD deficiency have significantly increased exposure to fluoropyrimidines.[8] It has also been found that overall survival and progression-free survival of DPD-deficient patients who preemptively receives a dose reduction were not negatively impacted.[9]

NCCN does not support routine screening. The NCCN Clinical Practice Guidelines in Oncology for Colon Cancer acknowledge evidence from published studies that support the feasibility, cost effectiveness, and improved safety of pretreatment DPD deficiency screening.[4,8,10] In the US, DPYD genotyping is the main test used to determine a DPD deficiency, which is defined as the presence of one or more variant DPYD alleles that are known to result in a DPD protein with partial or complete loss of function. However, the NCCN Panel for Colon/Rectal/Anal Cancers concludes that "because fluoropyrimidines are a pillar of therapy in [colorectal cancer] and it is not known with certainty that given DPYD variants are necessarily associated with this risk, universal pretreatment DPYD genotyping remains controversial and the NCCN Panel does not support it at this time."[4] See the **Sidebar** on page 3 for an editorial

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free option, parents of children who need this drug may have no other choice since pegfilgrastim injection is not available in a vial. If used in a hospital, pharmacists would be unlikely to dispense the prefilled syringe for administration when only a partial dose is prescribed. Instead, the exact dose would be prepared as a compounded sterile preparation following USP General Chapter <797>. That being said, this is a significant safety issue for outpatient pediatric patients receiving the drug, especially since not all pharmacists are aware of the issue.

One hospital-based specialty and retail pharmacy told us they provide patients with an empty sterile vial and a sterile syringe and needle. They instruct patients/caregivers to inject the entire contents of the prefilled pegfilgrastim syringe into the empty vial, withdraw the prescribed dose using the sterile syringe and needle, and discard the medication remaining in the vial. They have built standard instructions in the pharmacy computer system, and staff are now creating a standard teach-back process to confirm the patient's/caregiver's understanding and ability to withdraw the prescribed dose from the vial.

This is not ideal. For ongoing use in ambulatory care, some specialty/retail pharmacies may feel they have no choice but to dispense full syringes of the drug and have parents measure out the correct partial dose. In some cases, parents have accidentally given their child the full 6 mg dose. In one case, a 40 kg patient was prescribed Udenyca 4 mg, but because the syringe is not graduated, the family was unable to measure the dose. The prescriber eventually told the family to administer the full 6 mg. The organization that reported this event has added flags in their pharmacy system to promote patient counseling.

ISMP has contacted the US Food and Drug Administration (FDA) about this concern. Amgen and biosimilar manufacturers need to provide a vial presentation and/or add graduation marks to prefilled syringes so smaller doses can be measured. In conjunction with making a vial available, syringe manufacturers will need to make pediatric syringes available to deliver smaller doses.

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response to this article from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Panel for Colon/Rectal/Anal Cancers.

Other. It should also be mentioned that uridine triacetate (**VISTOGARD**) has been used to treat patients with pyrimidine toxicity due to DPD deficiency, even when given past 96 hours as recommended in the product labeling.[11] Such use, however, is not included in FDA-approved product labeling.

Conclusion

In reviewing the literature surrounding the hesitancy to adopt universal DPD deficiency screening prior to the use of fluoropyrimidines, the risk of patient harm and potential fatality seems clear when administering fluoropyrimidines to patients with a DPD deficiency, while the hurdles to implement widespread testing seem to be manageable. So, ISMP joins others who ask the question, "Why not?"

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Patient administration errors with the use of alprostadil urethral inserts

Patients have incorrectly used the product **MUSE** (acronym for medicated urethral suppository for erection), a urethral alprostadil suppository prescribed for erectile dysfunction. The medication is available preloaded in an applicator system (**Figure 1**) and is administered by inserting the stem into the urethra after urination (to ensure the urethra is wet) and pressing the applicator button. Each applicator system is wrapped in a foil pouch. Six applicator systems are packaged in a carton. Patients have reported confusion regarding how to properly use this product, resulting in ineffective medication and sometimes leading to urethral hemorrhage.

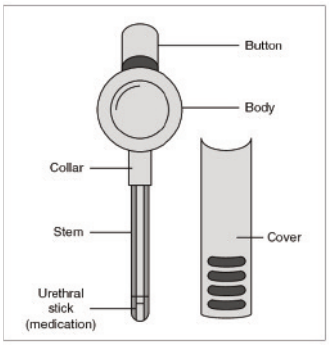

Figure 1. Muse applicator system.

One factor contributing to these errors has been the lack of adequate verbal patient education. Patients have reported that neither the prescriber nor the dispensing

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Why not screen for dihydropyrimidine dehydrogenase (DPD) deficiency in patients receiving fluorouracil or capecitabine?

Sidebar

The authors raise some important issues about screening for dihydropyrimidine dehydrogenase (DPD) deficiency; it is a complicated topic regarding a complex metabolic pathway. Our panel has discussed this issue extensively and we will continue to monitor any new developments in the literature.

There are a few comments we would like to make regarding DPD deficiency and pretreatment testing. The incidence of true total enzyme deficiency is probably less than 1% depending on the population while some level of deficient DPD activity occurs in about 5-10% of the population overall.[1] Deficient DPD activity is due to natural variations in the DPYD gene that make the patient less efficient in metabolizing the drug and its metabolites due to decreased activity of the patient's particular enzymes in the pathway.

In promoting pretreatment testing for DPYD variants, the authors cite studies which looked at a few specific variants and did show the benefits of pretesting in terms of diminishing the incidence of very severe fluorouracil associated toxicities. However, these studies provide no survival data to inform whether reducing the dose of fluorouracil by 50% at the start of treatment impacts efficacy, which is especially important when fluorouracil or capecitabine are being used in the adjuvant setting for patients with potentially curable cancer. If we had more precise dosing recommendations based on specific variations and survival data—if in fact dosing would be totally dependent on that particular enzyme variant—it would be a reasonable test to run. In fairness, these are small select studies, but we still need to know if we diminish the chance of a cure.

As for capecitabine, which is an oral prodrug, there are so many other variables regarding toxicities in individual patients, including age-related decreases in creatinine clearance, actual kidney disease

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pharmacist have explained how to administer the medication. In one case, the patient used the product with the protective cover still in place.

Another factor for confusion has been a breakdown in providing written instructions for use. Despite the professional package insert stating that "a Patient Package Insert (PPI) must be given to each patient at the initiation of therapy," patients are not always given one. This gap can be attributed to several issues. First, the manufacturer's information intended for patients, including step-by-step patient instructions for administration, is printed at the end of the professional package insert meant for healthcare professionals. Both pharmacists and patients could easily miss these essential patient instructions, and pharmacists may not give the patient what appears to be a professional package insert. Also, this information is confusingly referred to as "Patient Information" and not a "Patient Package Insert" as stated in the professional package insert. Another issue is that not all prescriptions are written for a quantity of six applicator systems, resulting in patients being dispensed individual foil pouches and not the full carton. As there appears to be only one package insert in the carton of six applicator systems, some patients will not receive the patient package insert when the carton is split. The current professional package insert with the included patient information could substitute for a separate PPI if there were enough of them and they were handed to each patient. Still, it would be far better if the "Patient Package Insert" was a document separate from the professional package insert and there were enough copies of the patient document to accommodate situations when individual pouches are dispensed.

For patients who do not receive the patient information, there are instructions on the back of each foil pouch that direct patients to two external manufacturer resources for information—the product-specific website (www.muserx.net) and a phone number to the company's medical information center. However, during the past several weeks, this website did not appear to be working, and the phone number did not lead to a direct line that walks patients through the administration process. In fact, we were unable to locate a functioning website or phone number for the manufacturer listed in the product labeling, Meda Pharmaceuticals of Somerset, NJ. The website needs to be made accessible as soon as possible, with separate updated instructions identified as a PPI. Also, direct telephone access needs to be available for patients who need their questions answered.

It is critical for prescribers and dispensing pharmacists to familiarize themselves with the administration process for Muse. They must teach patients how to administer the drug safely and verify the patient's understanding. They also must make sure to provide the patient with the manufacturer's professional package insert with the included patient information, if one is available. Other than diagrams in the product labeling, the manufacturer does not appear to provide additional information to help patients properly use Muse. There are, however, several useful videos about Muse on YouTube, including this one: www.ismp.org/ext/723. But the instructions may be challenging to find on YouTube because there are other products and a music artist using the name "Muse." It helps to include something else about the product in the search, such as "Muse suppository" or "Muse alprostadil."

ISMP has been in contact with the US Food and Drug Administration (FDA) regarding this product and the issues with the patient instructions. It should be mentioned that there are other medications and dosage forms packaged in cartons containing multiple units that may not be accompanied by an adequate number of PPIs if the carton is split to accommodate prescriptions for quantities less than a full carton. For products that are routinely dispensed in quantities less than a full carton (including Muse), manufacturers should consider including additional patient instructions for each individual drug product that might be dispensed. FDA should take this into account when interacting with manufacturers.

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and dysfunction, diet, and emerging data on the microbiome, that we would have no idea how to incorporate DPD findings into the dosing of that drug.

In summary, because of the integral role fluoropyrimidines play in the treatment of colon cancer, and the uncertainty regarding the impact of different DPYD variants on fluoropyrimidine metabolism and how dosing should be adjusted, the National Comprehensive Cancer Network (NCCN) panel does not support universal pretreatment DPYD genotyping at this time.

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