Medical Coverage Policy | Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer

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OVERVIEW

Variability in systemic exposure to 5-fluorouracil (5-FU) is thought to directly impact 5-FU tolerability and efficacy. The standard approach is dosing according to body surface area. Two alternative approaches have been proposed for modifying use of 5-FU: (1) dosing based on determined area under the curve serum concentration target and (2) genetic testing for variants affecting 5-FU metabolism. For genetic testing, currently available polymerase chain reaction tests assess specific variants in genes encoding dihydropyrimidine reductase (*DPYD*) and thymidylate synthase (*TYMS*) in the catabolic and anabolic pathways of 5-FU metabolism, respectively

MEDICAL CRITERIA

Not applicable.

PRIOR AUTHORIZATION

Not applicable.

POLICY STATEMENT

BlueCHiP for Medicare and Commercial

My5-FU™ testing or other types of assays for determining 5-fluorouracil area under the curve in order to adjust 5-fluorouracil (5-FU)dose for colorectal cancer patients or other cancer patients is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

Testing for genetic variants in dipyrimidine dehydrogenase (*DPYD*) or thymidylate synthase (*TYMS*) genes to guide 5-FU dosing and/or treatment choice in patients with cancer is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary.

BACKGROUND

The agent 5-fluorouracil (5-FU) is a widely used antineoplastic chemotherapy drug that targets thymidylate synthase (TYMS) enzyme, which is involved in DNA production. 5-FU has been used for many years to treat solid tumors (eg, colon and rectal cancer, head and neck cancer). In general, the incidence of grade 3 or 4 toxicity (mainly neutropenia, diarrhea, mucositis, and hand-foot syndrome) increases with higher systemic exposure to 5-FU. Several studies also have reported statistically significant positive associations between 5-FU exposure and tumor response. In current practice, however, 5-FU dose is reduced when symptoms of severe toxicity appear, but is seldom increased to promote efficacy.

Based on known 5-FU pharmacology, it is possible to determine a sampling scheme for area under the curve (AUC) determination and to optimize an AUC target and dose-adjustment algorithm for a particular 5-FU chemotherapy regimen and patient population. For each AUC value or range, the algorithm defines the dose adjustment during the next chemotherapy cycle most likely to achieve the target AUC without overshooting and causing severe toxicity.

In clinical research studies, 5-FU blood plasma levels most recently have been determined by high-performance liquid chromatography or liquid chromatography coupled with tandem mass spectrometry. Both methods require expertise to develop an in-house assay and may be less amenable to routine clinical laboratory settings.

Measuring Exposure to 5-FU

Laboratory Testing

Patient exposure to 5-FU is most accurately described by estimating the AUC, the total drug exposure over a defined period of time. 5-FU exposure is influenced by method of administration, circadian variation, liver function, and the presence of inherited dihydropyrimidine reductase (*DPYD*)–inactivating genetic variants that can greatly reduce or abolish 5-FU catabolism. As a result, both inter- and intrapatient variability in 5-FU plasma concentration during administration is high.

Determination of 5-FU AUC requires complex technology and expertise that may not be readily available in a clinical laboratory setting. In the United States, Saladax Biomedical offers a commercial immunoassay (My5-FU) that quantifies plasma 5-FU concentration from a blood sample drawn during continuous infusion at steady state (18-44 hours after the start of infusion) and provides a dose- adjustment algorithm to maintain plasma 5-FU AUC between 20 and 30 mg/h/L during the next cycle

Genetic Testing

5-FU is a pyrimidine antagonist, similar in structure to the normal pyrimidine building blocks of RNA (uracil) and DNA (thymine). More than 80% of administered 5-FU is inactivated and eliminated via the catabolic pathway; the remainder is metabolized via the anabolic pathway.
Catabolism of 5-FU is controlled by the activity of DPYD. Because DPYD is a saturable enzyme, the pharmacokinetics of 5-FU are strongly influenced by the dose and schedule of administration.2 For example, 5-FU clearance is faster with continuous infusion than with bolus administration, resulting in very different systemic exposure to 5-FU during the course of therapy. Genetic variants in *DPYD*, located on chromosome 1, can lead to reduced 5-FU catabolism and increased toxicity. Many variants have been identified (eg, IVS14+1G>A [also known as *DPYD*2A*], 2846A>T [D949V]). *DPYD* deficiency is an autosomal codominantly inherited trait.3
The anabolic pathway metabolizes 5-FU to an active form that inhibits DNA and RNA synthesis by competitive inhibition of *TYMS* or by incorporation of cytotoxic metabolites into nascent DNA.4 Genetic variants in *TYMS* can cause tandem repeats in the *TYMS* enhancer region (TSER). One variant leads to 3 tandem repeats (*TSER*3*) and has been associated with 5-FU resistance due to increased tumor *TYMS* expression compared with the *TSER*2* variant (2 tandem repeats) and wild-type forms.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). My5-FU™ (Saladax Biomedical) and genetic testing for variants in *DPYD* and *TYMS* for predicting risk of 5-fluorouracil toxicity and chemotherapeutic response (ARUP Laboratories) are available under the auspices of CLIA. (The LDT TheraGuide® by Myriad Genetics has been discontinued). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of laboratory or genetic tests for use of 5-FU.

For individuals who have cancer for whom treatment with 5-FU is indicated who receive laboratory assays to determine 5-fluorouracil area under the curve, the evidence includes randomized controlled trials (RCTs), observational studies, and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity and treatment-related morbidity. A systematic review of observational studies on analytic validity studies found good correlation between test results; however, reviewers concluded that

selected studies had high risk of bias due to excluded samples. Several analyses of patients with colorectal cancer have evaluated clinical validity. For example, 1 study found that the rate of severe toxicity was significantly lower in patients with stage II and III cancer who chose pharmacokinetic monitoring versus body surface area (BSA) monitoring, but progression-free survival did not differ between groups in patients with stage IV or recurrent cancer. No RCTs or nonrandomized comparative studies were identified comparing health outcomes in cancer patients who did and did not have 5-FU dose adjustment using the My5-FU assay and who were treated with chemotherapy regimens used in current clinical practice. A systematic review of the available literature found a significantly higher response rate with BSA-based monitoring and no significant difference in toxicity. Most data were from observational studies and the RCTs were conducted in the 1980s when different chemotherapy protocols were used. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer for whom treatment with 5-FU is indicated who receive genetic testing for variants (eg, in *DPYD* and *TYMS*) affecting 5-FU metabolism, the evidence includes observational studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity. A 2010 TEC Assessment concluded that *DPYD* and *TYMS* variant testing had poor prognostic capacity to identify patients likely to experience severe 5-FU toxicity. Since publication of that Assessment, no prospective trials comparing efficacy and toxicity outcomes in patients who did and did not undergo pretreatment *DPYD* and/or *TYMS* testing have been published. One study compared outcomes in patients undergoing pretreatment *DPYD* testing with historical controls who did not receive testing. In that study, rates of grade 3 or higher toxicity were lower in patients who had genetic testing; however, the study was not randomized and lacked concurrent controls. The evidence is insufficient to determine the effects of the technology on health outcomes.

CODING

BlueCHiP for Medicare and Commercial

The following code is not medically necessary.

S3722 Dose optimization by area-under-the-curve (AUC) analysis for infusional 5- fluorouracil (5-FU)

RELATED POLICIES

None

PUBLISHED

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