Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer

Variability in systemic exposure to 5-fluorouracil (5-FU) is thought to directly impact 5-FU tolerability and efficacy. Two approaches have been proposed for modifying use of 5-FU:

1. Dosing of 5-fluorouracil (5-FU) in cancer patients to a predetermined area under the curve (AUC) serum concentration target: Accurate AUC determination relies on sampling at a pharmacokinetically appropriate times, as well as on accurate methods of 5-FU serum concentration measurement. Available measurement methods are complex, making them less amenable to routine clinical laboratory settings.

2. Genetic testing for mutations affecting 5-FU metabolism: Genetic mutations may affect activity of enzymes involved in 5-FU metabolism. Currently-available polymerase chain reaction (PCR) tests assess specific mutations in genes encoding dihydروpyrimidine reductase (DPYD) and thymidylate synthase (TYMS), enzymes in the catabolic and anabolic pathways of 5-FU metabolism, respectively.

Background

5-Fluorouracil (5-FU) is a widely used antineoplastic chemotherapy drug that targets TYMS, an enzyme involved in DNA production. 5-FU has a narrow therapeutic index; doses recommended for effectiveness are often limited by hematologic and gastrointestinal toxicity. Moreover, patients administered the same fixed dose, continuous infusion regimen of 5-FU have wide intra- and inter-patient variability in systemic drug exposure, as measured by plasma concentration or, more accurately, by area under the curve techniques. AUC is a measure of the systemic drug exposure in an individual over a defined period of time.

In general, the incidence of grade 3 to 4 toxicity (mainly neutropenia, diarrhea, mucositis, and hand-foot syndrome) increases with higher systemic exposure to 5-FU. Several studies have also 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 seldom increased to promote efficacy.

Based on known 5-FU pharmacology, it is possible to determine a sampling scheme for 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 have most recently been determined by high-performance liquid chromatography or liquid chromatography coupled with tandem mass...
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spectrometry. Both methods require the expertise to develop an in-house assay and may be less amenable to routine clinical laboratory settings. One commercially available alternative is Saladax Biomedical’s My5-FU™, an immunoassay designed to measure patients' exposure to 5-FU to help oncologists adjust and optimize 5-FU dosing. My5-FU™ was originally marketed in the U.S. by Myriad Genetics as OnDose® under patents licensed from Saladax Biomedical (Bethlehem, PA). In June 2013, rights to the assay reverted to Saladax Biomedical.

Metabolism of 5-Fluorouracil

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. For example, 5-FU clearance is faster with continuous infusion compared with bolus administration, resulting in very different systemic exposure to 5-FU during the course of therapy. Genetic mutations 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.

• 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. Genetic mutations 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 in comparison with the TSER*2 variant (2 tandem repeats) and wild-type forms.

Myriad Genetics has developed a PCR test, TheraGuide®, to assess certain mutations in \(DPYD\) and \(TYMS\). The Myriad Genetics website estimates that “up to 25% of individuals have variations in the \(DPYD\) and/or \(TYMS\) genes that are associated with an increased risk of toxicity to 5-FU.” ARUP Laboratories also offers \(DPYD\) and \(TYMS\) mutation testing.

Regulatory Status

Currently, U.S. Food and Drug Administration (FDA)-approved tests for 5-FU AUC measurement and for \(DPYD/TYMS\) mutation testing are unavailable. My5-FU™ is offered by Saladax Biomedical as a laboratory-developed test; other clinical laboratories may offer in-house assays to measure 5-FU AUC. Similarly, TheraGuide® is offered by Myriad Genetics as a laboratory-developed test; other laboratories may offer in-house assays for \(DPYD\) and \(TYMS\) mutation testing (eg, ARUP Laboratories). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing. Both Saladax Biomedical and Myriad Genetics are CLIA-licensed laboratories.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***
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Policy

My5-FU™ testing or other types of assays for determining 5-fluorouracil area under curve in order to adjust 5-FU dose is considered investigational for all applications.

TheraGuide® testing for genetic mutations in dipyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) to guide 5-FU dosing and/or treatment choice in patients with cancer is considered investigational for all applications.

BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Laboratory and Genetic Testing for Use of 5-Fluorouracil is covered

Not applicable.

When Laboratory and Genetic Testing for Use of 5-Fluorouracil is not covered

My5-FU™ testing or other types of assays for determining 5-fluorouracil area under the curve in order to adjust 5-FU dose for colorectal cancer patients or other cancer patients is considered investigational.

TheraGuide® testing for genetic mutations in dipyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) to guide 5-FU dosing and/or treatment choice in patients with cancer is considered investigational.

Policy Guidelines

Prior evidence supports the wide variability of 5-fluorouracil (5-FU) plasma levels when patients are placed on a fixed-dose regimen; high exposure is associated with toxicity, but higher exposure up to the limits of toxicity is also associated with better tumor response to treatment. Area under the curve (AUC) laboratory testing methods to better measure 5-FU exposure during treatment of cancer and validated algorithms to modify subsequent dosing may improve response and reduce toxicity. However, currently available evidence is limited and insufficient to draw conclusions about the impact of 5-FU exposure measurement and AUC-targeted dose adjustment on outcomes of
patients administered contemporary chemotherapy regimens for colorectal or head and neck cancer. Given the lack of relevant studies, a similar conclusion is reached for use of 5-FU in other cancers.

Impaired function of enzymes in 5-FU metabolic pathways may contribute to toxicity and/or reduced efficacy. However, current evidence for pretreatment testing for genetic mutations in dihydropyrimidine dehydrogenase (DPYD) and/or thymidylate synthase (TYMS) comprises associational studies only. Impacts on treatment selection and 5-FU dosing have not been demonstrated. Evidence for improved outcomes in patients eligible for 5-FU chemotherapy is lacking.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: S3722.

There is no specific CPT coding for the TheraGuide testing. The following codes may be used: 81400 and 81401.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Medical Director – 4/2011


Senior Medical Director – 4/2014


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Policy Implementation/Update Information

5/10/11  New policy implemented. “OnDose™ testing or other types of assays for determining 5-fluorouracil area under the curve in order to adjust 5-FU dose for colorectal cancer patients or other cancer patients is considered investigational.” Medical Director review 5/29/2011. Notification given 5/10/2011. Policy effective date, 8/16/11. (btw)

9/30/11  Specialty Matched Consultant Advisory Panel review 8/31/2011. No change to policy. (btw)

1/1/12   Added new 2012 HCPCS code, S3722, to the “Billing/Coding” section. (btw)

5/1/12   Reference added. (btw)

9/4/12   Specialty Matched Consultant Advisory Panel review 8/15/2012. No change to policy. (btw)

5/14/13  Reference added. (btw)

9/10/13  Specialty Matched Consultant Advisory Panel review 8/21/2013. No change to policy. (btw)

4/29/14  Policy title changed from “Laboratory Testing to Allow Area Under the Curve (AUC) Targeted 5-Fluorouracil (5-FU) Dosing for Patients Administered 5-FU for Cancer” to “Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer”. Description section updated to change the name of OnDose® to My5-FU® and to add information regarding TheraGuide®. Additional non-coverage statement added to policy indicating: “TheraGuide® testing for genetic mutations in dipyrimidine dehydrogenase (DPYD) or thymidylate synthase (TYMS) to guide 5-FU dosing and/or treatment choice in patients with cancer is considered investigational.” Added the following statement to the When Not Covered section to indicate: “There is no specific CPT coding for the TheraGuide testing. The following codes may be used: 81400 and 81401. Policy Guidelines updated. Reference added. Senior Medical Director review 4/9/2014. Notification given 4/29/2014. Policy effective 7/1/2014. (btw)

9/9/14   Specialty matched consultant advisory panel review 8/26/2014. No change to policy statement. (lpr)

4/28/15  Reference added. (lpr)

10/1/15  Specialty Matched Consultant Advisory Panel review 8/26/2015. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.