

Corporate Medical Policy

Laboratory Testing to Allow Area Under the Curve (AUC) Targeted 5-Fluorouracil (5-FU) Dosing for Patients Administered 5-FU for Cancer

File Name: testing_to_allow_area_under_the_curve_targeted_5-fu_dosing
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Description of Procedure or Service

Dosing of 5-fluorouracil (5-FU) in cancer patients to a predetermined area under the curve (AUC) target has been proposed as a method to reduce variability in systemic exposure to 5-FU, reduce toxicity, and improve tumor response. Accurate AUC determination relies on sampling at a pharmacokinetically appropriate time, as well as on an accurate method of 5-FU laboratory measurement. Available measurement methods are complex and require the expertise to develop an in-house assay, making them less amenable to routine clinical laboratory settings. One commercially available alternative is Myriad Genetics' OnDose™, a diagnostic test that is designed to measure colorectal cancer patients' exposure to 5-FU, to help oncologists adjust and optimize 5-FU dosing and improve patient outcomes.

Background

5-Fluorouracil (5-FU) is a widely used antineoplastic chemotherapy drug with 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). 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 spectrometry. Both methods require the expertise to develop an in-house assay and may be less amenable to routine clinical laboratory settings.

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Regulatory Status

The OnDose™ test is offered by Myriad Genetics as a laboratory-developed test. Other clinical laboratories may offer in-house assays to measure 5-FU AUC. 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. Myriad Genetics is a CLIA-licensed laboratory.

*****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.**

Policy

OnDose™ 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. 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 Testing to Allow Area Under the Curve 5-FU Dosing is covered

Not applicable.

When Laboratory Testing to Allow Area Under the Curve 5-FU Dosing is not covered

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.

Policy Guidelines

5-Fluorouracil (5-FU) is a pyrimidine analog that is an antineoplastic antimetabolite; 5-FU has been useful for many years in the treatment of solid tumors, including colorectal adenocarcinoma. Potentiated by leucovorin (LV), 5-FU is the basis for several standard treatment regimens currently recommended by the National Comprehensive Cancer Network (NCCN) in the treatment of

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colorectal cancer. While it is recommended that adjuvant therapy for stage II colorectal cancer be limited primarily to disease with high-risk features and individualized for each patient, oxaliplatin in combination with 5-FU/LV is the preferred standard of care for treating patients with stage III disease. Based on the results of the European “Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer” (MOSAIC) trial in which the addition of oxaliplatin to a regimen of LV and infusional 5-FU every 2 weeks (i.e., a FOLFOX regimen) significantly increased disease-free (DFS) and overall survival (OS), the FOLFOX regimen is recommended for patients with stage III colorectal cancer. A FOLFOX regimen also improves progression-free survival (PFS) in patients with advanced (i.e., metastatic) colorectal cancer who are able to tolerate intensive versus single-agent 5-FU therapy. Other 5-FU-based combination chemotherapy regimens are also options in advanced disease. FOLFOX may also be considered for individual patients with high-risk stage II disease. In terms of administration, infusional 5-FU regimens are considered less toxic than bolus regimens and are inappropriate when administered with either irinotecan or oxaliplatin.

5-FU is a pyrimidine antagonist, similar in structure to the normal pyrimidine building blocks of RNA (uracil) and DNA (thymine). Approximately 85% or more 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 dihydropyrimidine dehydrogenase (DPD). Because DPD 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 to bolus administration, resulting in very different systemic exposure to 5-FU during the course of therapy.

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

Prior evidence supports the wide variability of 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 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, but currently available evidence is insufficient to support such testing.

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.

BCBSNC may request medical records for determination of medical necessity. When medical records are

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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

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.68, 2/10/2011

Medical Director – 4/2011

Specialty Matched Consultant Advisory Panel – 8/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.68, 3/8/2012

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)

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.