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Medical Policy Manual

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

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

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.

Background

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.

Regulatory Status

The OnDose™ test (Myriad Genetics) is offered commercially as a laboratory-developed test, designed to measure colorectal cancer patients' exposure to 5-FU to help oncologists adjust and optimize 5-FU dosing. Other clinical laboratories may offer in-house assays to measure 5-FU AUC. 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. Myriad Genetics is a CLIA-licensed laboratory.

MEDICAL POLICY CRITERIA

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**.

SCIENTIFIC EVIDENCE

Background

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.

As noted, determination of 5-FU AUC requires complex technology and expertise that may not be readily available in a clinical laboratory setting. In the U.S., Myriad Genetics offers a commercial service called OnDose™ that quantitates plasma 5-FU concentration from a blood sample drawn during continuous infusion at steady state, calculates AUC by multiplying 5-FU concentration by the infusion duration, and compares the results to a target AUC range established for colorectal cancer patients. According to information from Myriad's website, "OnDose test results are used to help optimize an individualized dose for the next cycle of 5-FU chemotherapy." Myriad technical

specifications for the 5-FU immunoassay describe the method and a summary of analytic validity data (replication, linearity, reportable range, interference, cross-reactivity, recovery, detection limit, stability, and comparison of methods), comparable to data summaries included in FDA-cleared diagnostic test kits. Review of the data indicates thorough technical validation and reasonable assay performance.[1] The OnDose™ test result itself does not include a dose adjustment algorithm, but the references for published algorithms are provided. Although searches of large clinical laboratories did not find tests for 5-FU AUC on their listings, it is possible that other clinical laboratories measure 5-FU levels by methods other than the specific method used by Myriad Genetics.

Modifying 5-Fluorouracil Exposure to Improve Outcomes

Evidence supporting the use of 5-FU AUC measurement to help modify subsequent 5-FU treatment doses in order to improve response and reduce toxicity has been summarized and evaluated in a BlueCross BlueShield Association Technology Evaluation Center (TEC) Special Report.[2] Early evidence from small, cohort studies showed that 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. This association has been studied extensively in head and neck cancer and in colorectal cancer. In addition, a majority of studies reported statistically significant positive associations between 5-FU exposure and tumor response.

Based on these early results, various strategies have been tried to reduce the variability in 5-FU pharmacokinetics, improve treatment efficacy, and decrease toxicity. In particular, individual pharmacokinetic dose adaptation can be accomplished by monitoring plasma 5-FU AUC at steady state during each treatment cycle and adjusting the administered 5-FU dose for the next treatment cycle to achieve a target AUC value established as maximally efficacious and minimally toxic. The hypothesis is that individual 5-FU dose modulation to a target AUC value that is just below the threshold for severe toxicity could minimize toxicity while improving response.

The results of single-arm trials of AUC-targeted 5-FU dose adjustment in advanced colorectal cancer patients suggested consistency of improved tumor response.[3-5] Similar, although less compelling results were seen in single-arm trials of AUC targeted 5-FU dosing in head and neck cancer.[6,7] The best contemporary evidence in support of AUC targeted dosing consists of two randomized, controlled trials (RCTs), one enrolling patients with colorectal cancer and the other, patients with head and neck cancer. No trials of any design were identified for 5-FU dose adjustment in other malignancies.

Gamelin et al.[3] developed a chart for weekly dose adjustment based on the results of an earlier, similar single-arm study[8] in which dose was increased by prespecified increments and intervals up to a maximum dose or the first signs of toxicity. In an RCT in patients with metastatic colorectal cancer, Gamelin et al.[9] reported significantly improved tumor response (33.6% versus 18.3%, respectively; p=0.0004) and a trend toward improved survival (40.5% versus 29.6%, respectively; p=0.08) in the experimental arm using AUC-targeted dosing. However, the authors also reported 18% grade 3 to 4 diarrhea in the fixed-dose control arm, higher than reported in comparable arms of two other large chemotherapy trials (5-7%).[10,11] In the latter two trials, delivery over a longer time period for both 5-FU (22 hours vs. 8 hours) and leucovorin (2 hours vs. bolus), which is characteristic of currently recommended 5-FU treatment regimens, likely minimized toxicity. The administration schedule used in the Gamelin et al.[9] trial is “rarely used in current practice in most countries” as described in an accompanying editorial by Walko and McLeod[12] and is absent from current guidelines.[13,14] Additional optimization studies are needed in order to apply 5-FU exposure monitoring and AUC-targeted dose adjustment to a more standard single-agent 5-FU treatment regimen. The new dose

adjustment scheme would then require validation versus a fixed-dose regimen in a comparative trial to ensure that tumor response is at least as good as or better than a fixed-dose regimen and toxicity is reduced. If the intent is to show that dose-modulated single-agent 5-FU is comparable to combination regimens such as fixed-dose FOLFOX, then FOLFOX should be added as a third treatment arm.

The same group more recently conducted a retrospective analysis of their dose adjustment protocol used in a FOLFOX regimen administered to patients with colorectal cancer (n=118) and compared with patients treated with FOLFOX administered in standard fashion according to body surface area (n=39).[15] In the dose-adjusted group, the therapeutic dose at 3 months was 110% of the theoretic dose. Grade 3/4 toxicity was 1.7% for diarrhea, 0.8% for mucositis, 18% for neutropenia, and 12% for thrombopenia; corresponding numbers were 12%, 15%, 25% and 10%, respectively, in the standard group. In the dose-adjusted group, the objective response rate was 70% at 3 months and 56% at 6 months; the corresponding result at 3 months for the standard group was 46%. Median overall survival and median progression-free survival in the dose-adjusted arm were 28 and 16 months, respectively; corresponding numbers for the standard group were 22 and 10 months. As the authors noted, this proof of principle study needs confirmation in a randomized trial.

Fety et al., in an RCT in patients with locally advanced head and neck cancer, used a different method of dose adjustment and reported overall 5-FU exposures in head and neck cancer patients that were significantly reduced in the dose adjustment arm compared to the fixed-dose arm.[16] This resulted in reduced toxicity but no improvement in clinical response. The dose adjustment method in this trial may have been too complex, as the 12 protocol violations in this treatment arm (of 61 enrolled) were all related to 5-FU dose adjustment miscalculations. Because patients with protocol violations were removed from analysis, results did not reflect the “real world” results of the dose adjustment method. In addition, the induction therapy regimen used two drugs, not the current standard of three; therefore, these results are also limited in generalizability to current clinical practice.

None of these trials used the OnDose™ test. For technical validation, OnDose was directly compared to liquid chromatography-tandem mass spectrometry[17]; the slope of the correlation was 1.03 (ideal: 1.00) and the r-value was 0.99 (ideal: 1.00). This test is clinically validated only for patients with colorectal cancer to determine 5-FU exposure and subsequent dose modification. Myriad Genetics cites Gamelin et al.[9] for clinical validation of AUC-targeted 5-FU dose adjustment and for information on how to modify the dose once 5-FU exposure has been determined. Gamelin et al. used high-performance liquid chromatography, similar to liquid chromatography-tandem mass spectrometry, to measure AUC. Thus, OnDose clinical validation is indirect; the only published clinical study using OnDose was reported in a commentary by Saam et al. describing the results of an observational analysis of sequential patients treated with constant infusion 5-FU using current adjuvant or metastatic treatment protocols with or without bevacizumab.[18] Samples were drawn at least 2 hours after the start of and before the end of each infusion and sent to Myriad Genetics Laboratories for analysis. Sixty-two patients were studied longitudinally across 4 sequential sample submissions (i.e., four 5-FU treatment infusions), of which only about 5% were within the target AUC after the first infusion. By the fourth infusion, this number rose to 37% and outliers were reduced. The use of bevacizumab did not affect results. No information on response or toxicity was reported.

Although several additional studies have been published, none were randomized comparisons.[18-20]

Given the limitations of the existing evidence, it is not possible to draw conclusions about the impact of 5-FU exposure measurement and AUC-targeted dose adjustment on health outcomes in patients

receiving contemporary chemotherapy regimens for colorectal, head and neck, or any other cancer. Given the lack of relevant studies, a similar conclusion is reached for use of 5-FU in other cancers.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN) Guidelines

The current evidence is limited to RCTs that investigate colon cancer and head/neck cancers. The NCCN guidelines for head/neck cancers and colon cancer do not address the use of area under the curve-guided 5-FU assays in order to adjust 5-FU dosing.[13,14]

Summary

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. While area under the curve laboratory testing is available, the current evidence is insufficient to support its use to measure 5-FU exposure during the treatment of any types of cancer. Because the impact of this testing on net health outcomes is not known, assays for determining area under the curve in order to adjust 5-FU dose for cancer patients, including but not limited to the OnDose™ test is considered investigational.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	84999	Unlisted chemistry procedure
HCPCS	S3722	Dose optimization by area-under-the-curve (AUC) analysis for infusional 5-fluorouracil (5-FU)