Medical Policy Manual Laboratory, Policy No. 06

In Vitro Chemoresistance and Chemosensitivity Assays

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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

In vitro chemoresistance and chemosensitivity assays have been investigated as a means of predicting tumor response to various chemotherapies.

MEDICAL POLICY CRITERIA

I. In vitro chemosensitivity assays, including but not limited to the histoculture drug response assay or a fluorescent cytoprint assay, ChemoFx assay, CorrectChemo assay, or EV3D from Kiyatec, are considered **investigational.**

II. In vitro chemoresistance assays, including but not limited to extreme drug resistance assays, are considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

These assays have been used by oncologists to select chemotherapy regimens for an

individual patient. A variety of assays have been developed that differ in their processing and in the technique used to measure chemotherapy sensitivity or resistance. All assays use characteristics of cell physiology to distinguish between viable and non-viable cells to quantify cell kill following exposure to a drug of interest and all involve the same four basic steps:

1. Isolation of cells
2. Incubation of cells with drugs
3. Assessment of cell survival
4. Interpretation of the results

Although a variety of assays exist to examine chemosensitivity or chemoresistance, only a few are commercially available. Available assays are outlined as follows:

METHODS USING DIFFERENTIAL STAINING/DYE EXCLUSION:

The Differential Staining Cytotoxicity (DiSC) assay relies on dye exclusion of live cells and involves cells treated with prospective chemotherapy agent(s) and drug sensitivity is measured by the amount of hematoxylin and eosin or fluorescein, respectively, which tumor cells selectively uptake.

The *Ex-vivo* Analysis of Programmed Cell Death (EVA/PCD™) assay (available from Rational Therapeutics) measures both apoptotic and non-apoptotic cell death markers in tumor samples exposed to chemotherapeutic agents. Tumor specimens obtained through biopsy or surgical resection are exposed to chemotherapy agents and then a mixture of Nigrosin B & Fast Green dye with glutaraldehyde-fixed avian erythrocytes are added to the cellular suspensions. The endpoint of interest for this assay is cell death as assessed by observing the number of cells differentially stained due to changes in cellular membrane integrity.

METHODS USING INCORPORATION OF RADIOACTIVE PRECURSORS BY MARCO-MOLECULES IN VIABLE CELLS:

The thymidine incorporation assay includes the addition of tritiated thymidine to the cell culture after 72 hours of incubation with the drug(s) of interest. By studying the inverse relationship between the amount of thymidine absorbed by viable tumor cells, drug sensitivity can be calculated.[1] The Extreme Drug Resistance assay (EDR®) (commercially available at Exiqon Diagnostics) is methodologically similar to the thymidine incorporation assay.[2] In this assay, tumor cells from an individual patient are cultured in soft agar and then exposed to high concentrations of selected chemotherapeutic agents for prolonged periods of time, far exceeding the exposure anticipated in vivo. Cell lines that survive this exposure are characterized by showing extreme drug resistance.

METHODS TO QUANTIFY CELL VIABILITY BY COLORMETRIC ASSAY:

The MTT assay, involves single tumor cell suspensions which are exposed to the chemical MTT. If the cell is metabolically active, blue crystals are produced. The Histoculture Drug Response Assay® (HDRA, commercially available from AntiCancer, Inc.) and the ChemoID® assay (available from Edwards Comprehensive Cancer Center) are types of MTT assays There is an inverse relationship between the drug sensitivity of the tumor and cell growth. Concentrations of drug and incubation times are not standardized and vary depending on drug combination and tumor type.

METHODS USING INCORPORATION OF CHEMOLUMINESCENT PRECURSORS BY

MARCO-MOLECULES IN VIABLE CELLS:

The Adenosine Triphosphate (ATP) Bioluminescence Assay relies on measurement of ATP to quantify the number of viable cells in a culture. Single cells or small aggregates are cultured, then exposed to drugs. Following incubation with the drug, cultured cells are lysed and ATP generation is captured with a luminometer, a device which measures light emitted from metabolic activity. From the measurement of light, the number of viable tumor cells can be calculated. A decrease in ATP indicates drug sensitivity, whereas no loss of ATP suggests that the tumor is resistant to the agent of interest. The ChemoFX® test (Precision Therapeutics) is an example of this technology.

METHODS USING DIFFERENTIAL OPTICAL DENSITY:

Similar to the EVA/PCD assay, this assay relies on measures of programmed cell death. In this assay, tumor cells are exposed to multiple concentrations of drugs and cultured. The optical density of the cells is measured over time, to create a density-by time curve. A sudden increase in optical density is associated with cell apoptosis; the extent of drug-induced apoptosis is a measure of the cell's sensitivity to that agent. The Microculture Kinetic (MiCK) Assay, also known as the CorrectChemo test, (Diatech Oncology, no longer commercially available) is an example of this technology.

Results may be reported as drug sensitive, drug resistant, or intermediate. Drugs identified as drug sensitive are thought to be potentially effective in vivo chemotherapies, while drugs identified as resistant are thought to be potentially ineffective chemotherapies. The rationale for chemosensitivity assays is strongest where there are a variety of therapeutic options and there are no clear selection criteria for any particular regimen in an individual patient.

REGULATORY STATUS

Commercially available chemosensitivity and chemoresistance assays are laboratory developed tests for which approval from the U.S. Food and Drug Administration (FDA) is not required when the tests are performed in a laboratory licensed by the Clinical Laboratory Improvement Act (CLIA) for high-complexity testing.

EVIDENCE SUMMARY

A 2000 BlueCross BlueShield Association Technology Evaluation Center (TEC) assessment reviewed both chemosensitivity and chemoresistance assays.[3] This TEC assessment provided a detailed discussion on what type of data would be required to validate the clinical use of chemoresistance and chemosensitivity assays and considered the following methods:

- Correlation studies based on in vitro prediction of in vivo response

  A variety of studies have reported a correlation between in vitro prediction or response and clinical response. While these studies may have internal validity, they cannot answer the question of whether patients given assay-guided therapy or empiric therapy have different outcomes. The principal outcomes associated with treatment of solid organ malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following

treatment. Patient quality of life may be another primary outcome. To determine whether assay-guided treatment results in different primary health outcomes, decision analysis or comparative trials are required.

- Decision analysis

  While decision analysis is a useful tool, it may be limited when the decision tree is so complex that it is not possible to obtain evidence-based estimates for many of the probabilities in the tree. For this reason, the 2000 TEC assessment concluded that decision analysis would not be a useful tool for assessing the relative effectiveness of assay-guided and empiric treatment.

- Assessment based on direct evidence

  Given the limitations in the above two techniques, the 2000 TEC assessment focused on direct evidence that compared outcomes for patients treated either by assay-guided therapy or contemporaneous empiric therapy. A total of seven studies were identified, none of which provided strong evidence to validate the clinical role of chemosensitivity or chemoresistance assays.

The BCBSA TEC Assessment was updated in 2002.[4] No studies were identified that address the limitations noted in the above discussion. Specifically, no studies were identified that provided direct evidence comparing outcomes for patients treated either by assay-guided therapy or contemporaneous empiric therapy.

CHEMORESISTANCE ASSAYS

In their assessment of chemoresistance assays, the authors of a 2004 systematic review of this type of testing pointed out that the clinical utility of these assays will depend on the prior probability of response to a given chemotherapy.[5] Since chemoresistance assays are used to deselect potential chemotherapies, the negative predictive value (NPV) is the key statistical measure. NPV relates to the likelihood that chemoresistance as measured in vitro will correspond to a lack of clinical effect. Unless the NPV is high, there is a chance that clinical decision-making based on a chemoresistance assay could inappropriately exclude an effective therapy. The NPV will vary according to the prior probability of chemoresistance. For example, the NPV in testicular cancer, typically a very chemosensitive tumor, will be lower than that associated with malignant melanoma, a very chemoresistant tumor. The TEC assessment concluded that chemoresistance assays have the highest clinical relevance in tumors with a low probability of response. However, it is still unclear how this information will affect clinical decision-making and whether health outcomes are improved as a result.

The extreme drug resistance (EDR) assay was specifically designed to produce a very high negative predictive value (>99%), such that the possibility of inappropriately excluding effective chemotherapy is remote in all clinical situations.[6] While the relevant clinical outcome in chemo*sensitivity* assays focuses on improved survival, the relevant outcome associated with chemo*resistance* assays is more controversial. Advocates of the EDR assay point out that avoidance of the toxicity of ineffective drugs is the relevant outcome, while others point out that this represents an intermediate outcome and that improved patient survival is the relevant outcome for chemoresistance assays.[6] For example, in clinical practice, deselection of one chemotherapy implies positive selection of another drug that did not show chemoresistance. Therefore, the toxicity and effectiveness of the drugs that are selected as a result of the EDR

assay are relevant outcomes. Finally, a related clinical outcome is the extent to which an in vitro assay can improve on the empirical performance of the physician. For example, chemoresistance typically can be predicted without the use of an EDR assay in heavily pretreated patients with refractory tumors. A literature search found no prospective comparative studies focusing on the use of the EDR or testing outcome with assay-directed therapy versus physician chosen therapy.

The bulk of the literature regarding extreme drug resistance assays have focused on nonrandomized correlation studies and associated reviews[7] that compare results from predictive in vitro assays with observed outcomes of chemotherapy.[8-21] However, in these studies, the patients do not receive assay-guided chemotherapy regimens. As discussed in the 2004 systematic review[5], correlational studies are inadequate for several reasons. First, such studies often aggregate patients with different tumor types, disease characteristics, chemotherapy options, and probabilities of response. This process is problematic since the accuracy of each assay used to predict in vivo response probably varies across different malignancies and patient characteristics. Second, the method by which assay results are translated into treatment decisions is not standardized. Without knowing the rules for converting assay findings into treatment choices, it is impossible to determine the effects of assay-guided treatment on health outcomes. Third, it is important to consider not only response, but also survival and adverse effects. The overall value of assay-guided therapy depends on the net balance of all health outcomes observed after treatment for all patients subjected to testing, regardless of the assay results or the accuracy of its predication for response.

Section Summary

Current evidence is insufficient to support the use of the EDR assays for directing therapy or for prediction of outcome. Current studies are limited by retrospective design, non-comparative design and small sample size. Furthermore, tissue samples are often not sufficient to achieve evaluable results. Large, randomized, prospective clinical studies comparing outcomes between assay-directed therapy to physician-directed therapy would be required to justify use of the EDR assay in these patient populations. The evaluation of overall and disease-specific survival, quality of life, and adverse events is critical to validate the clinical utility of these assays.

CHEMOSENSITIVITY ASSAY

The enthusiasm for chemosensitivity assays has diminished over the years, due to the poor positive predictive values (PPV), the key statistical measure for this type of assay. PPV relates to the likelihood that drugs shown to be effective in vitro will produce a positive clinical response. For example, a meta-analysis by Von Hoff (1990) of 54 retrospective studies reported a PPV of only 69%.[22] The poor PPV may be related to a variety of host factors, such as tumor vascularity, poor quality of data, or tumor sampling bias. Several prospective trials have also been published, although interpretation of their findings is hindered by technical challenges, inconclusive results, or methodologic issues.[23-36] For example, Xu (1999) compared outcomes for a chemosensitivity assay-guided treatment group with outcomes for a group given contemporaneous empiric therapy.[26] The patient sample consisted of 156 patients with advanced breast cancer. The article stated that choice of regimen in the assay-guided group was based on assay results, but no specific decision rules were reported. Patients whose assay results suggested resistant disease were given empiric regimens and

were excluded from the analysis of outcome results, violating the principles of intention-to-treat analysis. An intention-to-treat analysis is the most robust analysis to control for bias and permits investigators to calculate the number of patients needed to test to identify one patient whose outcomes could be improved by use of assay-guided rather than empiric therapy.

In 2015, Zhang evaluated ovarian epithelial cancer cells using an in vitro ATP tumor chemosensitivity assay[37]. Specimens from 80 women with OAC who had undergone cytoreductive surgery were tested for sensitivity to 8 different treatments (paclitaxel, carboplatin, topotecan, gemcitabine, docetaxel, etoposide, bleomycin, 4-hydroperoxycyclophosphamide). Overall sensitivity, specificity, positive predictive value, and negative predictive value were 88.6%, 77.8%, 83.0%, and 84.8%, respectively. Specimens from the lower stage (I-II) ovarian epithelial cancer had lower chemosensitivity than advanced stage (III). High to mildly differentiated specimens had lower chemosensitivity than low differentiated specimens.

In the only prospective, randomized study published since the TEC assessments, Cree (2007) reported on a chemosensitivity assay-directed chemotherapy versus physician's choice in patients with recurrent platinum-resistant ovarian cancer.[38] Response rate and progression-free survival were studied in 180 patients randomized to either ATP-based tumor chemosensitivity assay-directed therapy (n=94) or physician's-choice chemotherapy (n=86). Median follow-up at analysis was 18 months; response was assessable in 147 (82%) patients: 32% achieved a partial or complete response in the physician's-choice group compared with 41% in the assay-directed group (26% vs. 31% by intention-to-treat analysis, respectively). Intention-to-treat analysis showed no statistically significant differences between the groups in terms of progression-free survival (93 days in the physician's-choice group vs. 104 days in the assay-directed group), nor any difference in overall survival between the groups. The authors concluded that this small randomized, clinical trial documented a trend toward improved response and progression-free survival for assay-directed treatment and that chemosensitivity testing might provide useful information in some patients with ovarian cancer. They also noted that the ATP-based tumor chemosensitivity assay remains an investigational method in this condition.

Section Summary

The current evidence is insufficient to permit conclusions regarding the benefit of chemosensitivity assays to predict a positive clinical response for a specific chemotherapy. Current studies are limited by retrospective design[39], non-comparative design, and small sample size[40]. Large, randomized, prospective clinical studies are needed to assess how assay-directed therapy compares with physician-directed therapy in predicting positive therapy response and improving overall health outcomes.

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

The 2011 ASCO guidelines does not recommend the use of chemotherapy sensitivity and resistance assays, unless in a clinical trial setting.[41]

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) Guidelines for the Treatment of

Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (V1.2024) state: “Chemosensitivity/resistance and/or other biomarker assays are being used at some NCCN Member Institutions for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is not sufficient to supplant standard-of-care chemotherapy (category 3)[42].”

SUMMARY

There is not enough research to show that chemoresistance and chemosensitivity assays improve chemotherapy treatment decisions or overall health outcomes for patients with cancer. Also, no clinical practice guidelines recommend the use of these assays. Therefore, the use of chemoresistance and chemosensitivity assays for the selection of chemotherapy treatment, or any other indication, is considered investigational.

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CODES

Codes	Number	Description
CPT	0564T	Oncology, chemotherapeutic drug cytotoxicity assay of cancer stem cells (CSCs), from cultured CSCs and primary tumor cells, categorical drug response reported based on percent of cytotoxicity observed, a minimum of 14 drugs or drug combinations
	0083U	Oncology, response to chemotherapy drugs using motility contrast tomography, fresh or frozen tissue, reported as likelihood of sensitivity or resistance to drugs or drug combinations
	0248U	Oncology, spheroid cell culture in a 3D microenvironment, 12-drug panel, brain – or brain metastasis-response prediction for each drug
	0435U	Oncology, chemotherapeutic drug cytotoxicity assay of cancer stem cells (CSCs), from cultured CSCs and primary tumor cells, categorical drug response reported based on cytotoxicity percentage observed, minimum of 14 drugs or drug combinations
	0511U	Oncology (solid tumor), tumor cell culture in 3D microenvironment, 36 or more drug panel, reported as tumor-response prediction for each drug
	81535	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination
	81536	;each additional single drug or drug combination (List separately in addition to code for primary procedure)
	86849	Unlisted immunology procedure
	84999	Unlisted chemistry procedure
	87999	Unlisted microbiology procedure
	88199	Unlisted cytopathology procedure
	89240	Unlisted miscellaneous pathology test
HCPCS	None	

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