Blue Cross Blue Shield of Rhode Island

EFFECTIVE DATE: 09|04|2007
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OVERVIEW

In vitro chemoresistance and chemosensitivity assays have been investigated as a means of predicting tumor response to various chemotherapies. These assays have been used by oncologists to select chemotherapy regimens for individual patients. This policy documents the coverage determination for the use of assay tests to predict tumor response to various chemotherapies.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

BlueCHiP for Medicare and Commercial Products

In vitro chemosensitivity assays and chemoresistance assays are considered not medically necessary as the data are insufficient to determine whether use of the tests to select chemotherapy regimens for individual patients will improve outcomes.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for limitations of benefits/coverage when services are not medically necessary.

BACKGROUND

A variety of chemosensitivity and chemoresistance assays have been clinically evaluated in human trials. All assays use characteristics of cell physiology to distinguish between viable and non-viable cells to quantify cells killed following exposure to a drug of interest. With few exceptions, drug doses used in the assays are highly variable depending on tumor type and drug class, but all assays require drug exposures ranging from several-fold below physiologic relevance to several-fold above physiologic relevance. Although a variety of assays exist to examine chemosensitivity or chemoresistance, only a few are commercially available. These available assays are outlined as follows:

Methods using differential staining/dye exclusion:

- *The Differential Staining Cytotoxicity assay*. This assay relies on dye exclusion of live cells after mechanical disaggregation of cells from surgical or biopsy specimens by centrifugation. Cells are then established in culture and treated with the drugs of interest at 3 dose levels; the middle dose is that which could be achieved in therapy; 10-fold lower than the physiologically relevant dose; and 10-fold higher. Exposure time ranges from 4 to 6 days; then, cells are restained with fast green dye and counterstained with hematoxylin and eosin (H&E). The fast green dye is taken up by dead cells, and H&E can then differentiate tumor cells from normal cells. The intact cell membrane of a live cell precludes staining with the green dye. Drug sensitivity is measured by the ratio of live cells in the treated samples to the number of live cells in the untreated controls.

- *The EVA/PCD™ assay* (available from Rational Therapeutics). This assay relies on ex vivo analysis of programmed cell death, as measured by differential staining of cells after apoptotic and nonapoptotic cell death markers in tumor samples exposed to chemotherapeutic agents. Tumor specimens obtained through biopsy or surgical resection are disaggregated using DNase and collagenase IV to yield tumor clusters of the desired size (50-100 cell spheroids). Because these cells are not proliferated, these microaggregates are believed to more closely approximate the human tumor microenvironment. These cellular aggregates are treated with the dilutions of the chemotherapeutic drugs of interest and incubated for 3 days. After drug exposure is completed, a mixture of Nigrosin B & Fast green dye with glutaraldehyde-fixed avian erythrocytes is added to the cellular suspensions. The samples are then agitated and cytospin-centrifuged and, after air drying, are counterstained with H&E. The end point 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.

- *The fluorometric microculture cytotoxicity assay*. This is another cell viability assay that relies on the measurement of fluorescence generated from cellular hydrolysis of fluorescein diacetate to fluorescein in viable cells. Cells from tumor specimens are incubated with cytotoxic drugs; drug resistance is associated with higher levels of fluorescence.

Methods using incorporation of radioactive precursors by macromolecules in viable cells:

- Tritiated thymine incorporation measures uptake of tritiated thymidine by DNA of viable cells. Using proteases and DNAse to disaggregate the tissue, samples are seeded into single-cell suspension cultures on soft agar. They are then treated with the drug(s) of interest for 4 days. After 3 days, tritiated thymidine is added. After 24 hours of additional incubation, cells are lysed, and radioactivity is quantified and compared with a blank control consisting of cells that were treated with sodium azide. Only cells that are viable and proliferating will take up the radioactive thymidine. Therefore, there is an inverse relationship between update of radioactivity and sensitivity of the cells to the agent(s) of interest.

- The Extreme Drug Resistance assay (EDR®)6 (Exiqon Diagnostics, Tustin, CA; no longer commercially available) is methodologically similar to the thymidine incorporation assay, using metabolic incorporation of tritiated thymidine to measure cell viability; however, single cell suspensions are not required, so the assay is simpler to perform. Tritiated thymidine is added to the cultures of tumor cells, and uptake is quantified after various incubation times. Only live (resistant) cells will incorporate the compound. Therefore, the level of tritiated thymidine incorporation is directly related to chemoresistance. The interpretation of the results is unique in that resistance to the drugs is evaluated, as opposed to evaluation of responsiveness. Tumors are considered to be highly resistant when thymidine incorporation is at least 1 standard deviation above reference samples.

Methods to quantify cell viability by colorimetric assay:

- The Histoculture Drug Resistance Assay (HDRA; AntiCancer Inc., San Diego, CA). This assay evaluates cell growth after chemotherapy treatment based on a colorimetric assay that relies on mitochondrial dehydrogenases in living cells. Drug sensitivity is evaluated by quantification of cell growth in the 3-dimensional collagen matrix. 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 macromolecules in viable cells:

- The Adenosine Triphosphate (ATP) Bioluminescence assay. This assay relies on measurement of ATP to quantify the number of viable cells in a culture. Single cells or small aggregates are cultured, and then exposed to drugs. Following incubation with drug, the cells are lysed and the cytoplasmic components are solubilized under conditions that will not allow enzymatic metabolism of ATP. Luciferin and firefly luciferase are added to the cell lysis product. This catalyzes the conversion of ATP to adenosine di- and monophosphate, and light is emitted proportionally to metabolic activity. This is quantified with a

luminometer. From the measurement of light, the number of 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.

- ChemoFX® (Helomics Corp., previously called Precision Therapeutics, Pittsburgh, PA). This assay also relies on quantifying ATP based on chemoluminescence. Cells must be grown in a monolayer rather than in a 3-dimensional matrix.

Methods using differential optical density:

- CorrectChemo® (previously called the Microculture Kinetic [MiCK)] assay; DiaTech Oncology, Franklin, TN). Similar to the EVA/PCD assay, this assay relies on measures of programmed cell death. In the 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 rationale for chemosensitivity assays is strongest when there are a variety of therapeutic options and there are no clear selection criteria for any particular regimen in an individual patient.

There are only a few comparative studies that evaluate use of a chemosensitivity assay to select chemotherapy versus standard care, and these studies do not report significant differences in outcomes between groups. A larger number of studies have used correlational designs that evaluate the association between assay results and already known patient outcomes. These studies report that results of chemosensitivity and chemoresistance assays are predictive of outcomes. However, these studies do not evaluate whether these assays lead changes in management and whether any changes in management lead to improved outcomes. In addition, interpretation of these studies is limited by heterogeneity in test methodology, tumor type, patient population, and chemotherapeutic agents. As a result, the clinical utility of chemoresistance and chemosensitivity assays has not been determined, and data are insufficient to determine whether use of the test to select chemotherapy regimens for individual patients will improve outcomes. Therefore, this testing is considered not medically necessary.

CODING

BlueCHiP for Medicare and Commercial Products

There is no specific CPT code for these assays as the extreme drug resistance assay is a multistep laboratory procedure that might be identified by several codes. Claims should be filed with an unlisted code.

RELATED POLICIES

None

PUBLISHED

Provider Update, October 2015
Provider Update, October 2014
Provider Update, December 2013
Provider Update, August 2012
Provider Update, September 2011
Provider Update, November 2010
Provider Update, October 2009
Provider Update, October 2008

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