

American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Chemotherapy Sensitivity and Resistance Assays

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Editor's Note: This is the complete American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update and provides the recommendations with comprehensive discussions of the relevant literature for recommendation(s). Data supplements with evidence tables, as well as other tables and figures, are available at <http://www.asco.org/guidelines/csr>.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose

To update the American Society of Clinical Oncology (ASCO) Technology Assessment guidelines on chemotherapy sensitivity and resistance assays (CSRAs) published in 2004.

Methods

An Update Working Group reviewed data published between December 1, 2003, and May 31, 2010. MEDLINE and the Cochrane Library were searched. The literature search yielded 11,313 new articles. The limits for "human and English" were used, and then standard ASCO search strings for randomized controlled trials, meta-analyses, guidelines, and reviews were added, yielding 1,298 articles for abstract review. Of these, only 21 articles met predefined inclusion criteria and underwent full text review, and five reports of randomized controlled trials were included for data extraction.

Results

Review of the literature does not identify any CSRAs for which the evidence base is sufficient to support use in oncology practice.

Recommendations

The use of CSRAs to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations based on published reports of clinical trials and a patient's health status and treatment preferences. Because the in vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority.

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) Technology Assessment: Chemotherapy Sensitivity and Resistance Assays¹ was first published in 2004. ASCO guidelines (some previously titled Technology Assessments) are updated at intervals, and this update reflects new evidence but no change in the recommendations from the original guideline. It summarizes the updated literature and includes a brief discussion.

The 2011 recommendations are the same as the original 2004 recommendations and are as follows. The use of chemotherapy sensitivity and resistance assays (CSRAs) to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations on the basis of published reports of clinical trials and a

patient's health status and treatment preferences. Because the in vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority.

BACKGROUND

CSRAs are in vitro laboratory analyses of sample cells taken from a primary tumor or from a metastatic tumor (before or after treatment with chemotherapy) to provide predictive information regarding a tumor's particular chemotherapy sensitivity or resistance. CSRAs have been studied as a means of enhancing patient selection for a specific treatment and/or to avoid drugs to which a tumor is resistant. In this update, studies in which treatments after CSRAs were used were contrasted with studies of empiric therapy (when a physician chooses a drug or regimen based on expected clinical outcomes) reported

in the existing literature. This update, like the original guideline, focuses exclusively on CSRAs performed on viable patient tumor tissue and does not address the utility of assays performed on nonviable tumor tissues using immunohistochemistry, gene expression, transcript profiling, or other diagnostic approaches.

UPDATE METHODOLOGY

For the 2011 Update, an ASCO Update Committee/Working Group (Appendix Table A1, online only) was composed of members of the full 2004 original CSRA Guideline Panel. They completed the review and analysis of data published in English in MEDLINE and the Cochrane Collection Library from December 2003 to May 2010. An evidence table with data from the new studies is provided as a Data Supplement. An overview of the CSRAs, as it appeared in the original guideline, is provided as a Data Supplement. The literature searches, a quorum diagram with details about the number of excluded and included publications, and the original guideline questions (same inclusion and exclusion criteria in 2011 Update) are also provided as Data Supplements. The Working Group of the Update Committee drafted the manuscript and circulated it via e-mail to the full Update Committee for review and approval. ASCO's Clinical Practice Guideline Committee leadership reviewed and approved the final document.

Guideline Policy

The practice guideline is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This guideline does not

THE BOTTOM LINE
ASCO GUIDELINE UPDATE
Use of Chemotherapy Sensitivity and Resistance Assays (CSRAs) for Patients With Cancer
Intervention
<ul style="list-style-type: none"> • Use of CSRAs to determine chemotherapy
Target Audience
<ul style="list-style-type: none"> • Medical Oncologists
Recommendation
<ul style="list-style-type: none"> • CSRAs to select chemotherapeutic agents for individual patients are not recommended outside of the clinical trial setting
Methods
<ul style="list-style-type: none"> • Systematic review and analysis of the medical literature by an Update Committee
Data supplements, including evidence tables, and clinical tools and resources can be found at www.asco.org/guidelines/csra

Table 1. 2004 and 2011 Recommendations

Recommendation Category	2004 and 2011 Recommendations
Use of CSRAs	The use of CSRAs to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting.
Chemotherapy treatment decisions	Oncologists should make chemotherapy treatment recommendations on the basis of published reports of clinical trials and a patient's health status and treatment preferences.
Future research: evaluating CSRAs in clinical trials	Because the in vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority.
Abbreviation: CSRA, chemotherapy sensitivity and resistance assays.	

recommend any particular product or course of medical treatment. Use of the practice guideline is voluntary.

Guideline and Conflict of Interest

The Update Committee was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines (summarized at <http://www.asco.org/guidelinescoi>). Members of the Update Committee completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Conflict of Interest Management Procedures, the majority of the members of the Update Committee did not disclose any such relationships.

SUMMARY OF LITERATURE REVIEW RESULTS

The relevant literature was identified using the search strategy outlined in the Data Supplement. As with the previous ASCO guideline on CSRAs, the following criteria for selection were applied to each publication: inclusion and exclusion criteria included outcome comparisons (prospective or retrospective) for patients whose chemotherapy was chosen empirically (based on clinical trial literature) as opposed to selection based on results of CSRAs; CSRA performance on viable patient tumor tissue as opposed to other forms of diagnostic testing performed on nonviable tumor tissue; a study sample size of ≥ 20 patients per arm; and primary end points of cancer events or survival including overall survival (OS) and/or response to therapy, disease-free survival, progression-free survival, local tumor control, and/or treatment toxicity.

After a careful review of the literature, data were extracted for the following CSRAs: adenosine triphosphate bioluminescence (ATP; $n = 2$ publications),^{2,3} extreme drug resistance assay (EDRA; $n = 1$ publication),⁴ methyl-thiazolyl-diphenyl-tetrazolium bromide (MTT; $n = 1$ publication),⁵ and ChemoFX (Precision Therapeutics, Pittsburgh, PA; $n = 1$ publication).⁶ Following is a synopsis of each of these publications.

ATP Assay

Cree et al² randomly assigned 180 patients (147 patients [82%] were evaluable) with recurrent ovarian cancer to assay-directed chemotherapy (n = 94) or empirical, physician-directed chemotherapy (n = 86). In the empirical group, 31.5% of patients achieved partial or complete response, whereas in the assay-directed group, 40.5% of patients achieved a response. Patients in assay-directed group were more likely than patients in the physician-directed group to receive combination therapy versus single-agent therapy (88% v 64%, respectively; *P* = not significant), which may account for the higher response rate in the assay-directed cohort. No significant differences were seen in progression-free survival or OS. These data are insufficient to change the conclusions in the original guideline.

Data are included in the Data Supplement from a published multicenter phase II randomized controlled trial by Ugurel et al³ that investigated the efficacy of assay-directed, first-line chemotherapy for melanoma patients (with no distinct alternative to empirical therapy for these patients) using an ATP assay for patients with metastasis. The study groups were divided into 22 chemotherapy-sensitive patients (42%) and 31 chemotherapy-resistant patients (58%). Objective response and OS were 36.4% and 14.6 months, respectively, in the chemotherapy-sensitive group, whereas the objective response and OS were 16.1% and 7.4 months, respectively, in the chemotherapy-resistant group. However, the investigators did not compare the two therapeutic interventions. A phase III study has been proposed.

MTT Assay

Wu et al⁵ retrospectively reviewed (nonrandomized comparison) and analyzed results of 353 consecutive patients with gastric cancer who received MTT-directed chemotherapy (n = 157) or physician’s empirical chemotherapy (n = 196); the survival rates were 47.5% and 45.1%, respectively. No statistically significant difference in survival between the two groups was observed.

EDRA

Joo et al⁴ evaluated 78 patients (nonrandomized comparison) with ovarian cancer, with 39 patients in the EDRA group and 39 patients in the physician’s choice/empiric therapy group; the overall response rates were 84.5% and 71.8%, respectively. There have been

other recent studies but with no empiric control group evaluating the utility of EDRA.

ChemoFX Assay

The Update Working Group considered data from recently published studies using the ChemoFX assay. This assay has not been prospectively compared with other cellular or molecular chemotherapy response tests or a clinical gold standard. Further research may establish it as an assay for clinical use, but data are not sufficient to recommend routine use of ChemoFX outside of clinical trials. Two retrospective cases series correlated the results of ChemoFx with cancer-free survival in patients with ovarian cancer, and one small series correlated its results with pathologic complete response of small breast lesions to neoadjuvant therapies.^{6,7} The studies had methodologic limitations including being case series with potential selection and observational biases, lack of blinding, lack of comparison groups, selection of chemotherapy at the discretion of the treating physician, and the confounding use of results of the assay to help determine the treatment regimen.

A detailed evidence table, entitled “Summary of Findings of New Studies Evaluating the Clinical Utility of CSRA,” is provided as a Data Supplement.

2011 GUIDELINE RECOMMENDATIONS

The Update Committee determined that no changes to the 2004 recommendations are warranted. These recommendations are listed in Table 1.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Administrative support: Pamela B. Mangu, Mark R. Somerfield

Manuscript writing: All authors

Final approval of manuscript: All authors

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Appendix**Table A1.** 2011 Update Committee for American Society of Clinical Oncology Update on the Use of Chemotherapy Sensitivity and Resistance Assays

Update Committee Members	Affiliation/Institution
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