THE BOTTOM LINE

ASCO GUIDELINE UPDATE

Intervention

- Antiemetics for patients receiving cancer therapy

Target Audience

- Medical oncologists, radiation oncologists, oncology nurses

Key Recommendations

- Patients who receive highly emetic chemotherapy regimens should receive the three-drug combination of a neurokinin 1 (NK₁) antagonist, 5-hydroxytryptamine-3 (5-HT₃) receptor antagonist, and dexamethasone.
- The preferred 5-HT₃ receptor antagonist for patients who receive moderate emetic chemotherapy regimens is palonosetron; antiemetic treatment includes that agent combined with a corticosteroid.
- Antiemetic treatment for patients who receive combination chemotherapy should be determined according to the agent with the greatest degree of emetic risk.
- Both dexamethasone and a 5-HT₃ antagonist are recommended for patients undergoing high-dose chemotherapy.
- Pediatric patients receiving either high or moderate emetic risk chemotherapy should be treated with a 5-HT₃ antagonist and corticosteroids; higher weight-based dosing may be required.
- For those treated with high emetic risk radiation therapy, a 5-HT₃ antagonist before each fraction and a 5-day course of dexamethasone are recommended.
- A 5-HT₃ antagonist before each fraction is also recommended before moderate-risk radiation; a 5-day course of dexamethasone is optional.
- For patients who receive combination chemoradiotherapy, antiemetic therapy is dictated by the emetogenicity of chemotherapy, unless the emetic risk of radiation therapy is higher.

Methods

- A systematic review of the literature published since the last update of the guideline.

Additional Information

- An Executive Summary of this guideline was published in *Journal of Clinical Oncology*

Data supplements, including evidence tables, and clinical tools and resources can be found at www.asco.org/guidelines/antiemetics.

Commentary: Should Cost and Comparative Value of Treatments Be Considered in Clinical Practice Guidelines?

By Ethan Basch, MD, MSc, Mark R. Somerfield, PhD, Ann Partridge, MD, MPH, Lowell Schnipper, MD, and Gary H. Lyman, MD, MPH

The cost of cancer treatment in the United States is increasing and has become a topic of national debate.¹ On average, US health care expenditures have grown more rapidly over the past three decades than in any other major industrialized nation. Cancer diagnostics and therapeutics constitute a substantial proportion of these costs. It is therefore critical to aggregate and evaluate evidence related to the effectiveness, safety, and relative value of treatments, toward informing clinical and policy decisions.

But it remains unclear which stakeholders in the continuum of oncology care—including policy makers, drug manufacturers, regulators, compendia developers, payers, specialty society-affiliated guideline developers, health care/hospital networks, clini-

cians, and/or patients—should participate in establishing whether a particular treatment or management approach offers better value for the money compared with other options (Table 1). Uneven attempts to define value, and lack of agreement on standards to do so, have led to inconsistent pricing and coverage policies.

For example, the Centers for Medicare & Medicaid Services (CMS) recently opted to continue coverage for bevacizumab (Avastin) in metastatic breast cancer despite results from randomized controlled trials that failed to demonstrate any survival advantage, and a unanimous vote by a US Food and Drug Administration (FDA) Advisory Committee not to sustain approval for this indication. CMS also recently conducted a review of coverage for Sipuleucel-T (Provenge) in metastatic

Table 1. Extent of Consideration of Cost Effectiveness by Various Stakeholders Involved With the Approval, Evaluation, and Distribution of Cancer Drug/Biologic Products

Stakeholders	Consideration of Cost Effectiveness
FDA	No. Does not consider costs of products in approval process.
Compendia	No. Generally do not consider costs of products in listing processes.
Drug product manufacturers	Limited. Set prices to support product development and compensate investors/shareholders, based on perception of market demand.
Centers for Medicare & Medicaid Services	No. Pay for indications approved by FDA or listed in compendia regardless of cost effectiveness.
Private payers	Variable. Pay for indications approved by FDA and generally when listed by compendia; may include internal review processes which limit or prioritize choices based on cost.
Specialty society–affiliated clinical practice guideline developers	Limited. Most guidelines only consider efficacy/effectiveness, and variably consider harms. Cost effectiveness generally not considered.
Health care/hospital networks	Variable. May limit or prioritize choices on the basis of cost.
Clinicians	Limited. Guidelines often encourage clinicians to consider and discuss costs with patients, but inadequate information about costs is often available to support cost effectiveness–based decision making at the individual clinician or patient level.
Patients	No. Prohibitive out-of-pocket expenses for some patients may guide choices, but costs of products generally do not guide decisions of insured individuals.
Policy makers	Limited. Recent health care legislation largely avoids cost effectiveness, and prohibits its consideration in some coverage decision contexts.

Abbreviation: FDA, US Food and Drug Administration.

prostate cancer, a process that attracted attention as a possibly veiled attempt to curb costs, an allegation the agency denied. Sipuleucel-T is priced at \$93,000 per course, with a median survival advantage of approximately 4 months. In the context of intense external pressure, a decision was rendered to cover the product when used within its FDA-defined indication.

CMS and private payers generally cover products approved by the FDA, at prices set by the manufacturers. The FDA and their advisors are prohibited from considering cost when evaluating products. Manufacturers are under internal and external pressure to price drugs to recoup expensive development costs, to subsidize exploration of products that never make it to market, and to satisfy investors or shareholders. CMS and private payers may also cover off-label use of products listed in one of several designated compendia, including the National Comprehensive Cancer Network Drugs & Biologics Compendium. These compendia do not consider cost and use inconsistent methodologies for listing treatments.² Private payers may develop internal guidelines that limit or prioritize coverage on the basis of cost or cost-effectiveness beyond what is listed in compendia.

The current national discussion around comparative effectiveness research (CER) is moving toward identifying optimal strategies to deliver the most effective and safe interventions in the most efficient way. A goal of CER in oncology is to gather available evidence to address critical questions related to the benefits, harms, and overall value of interventions.^{3,4} Although sometimes confused with rationing, such efforts, appropriately guided by clinical and patient perspectives, can identify which approaches offer the greatest value to patients, and can inform rational, clinically valid, evidence-based choices to improve the health care of individuals and society.

Historically, guidelines from ASCO have not considered costs in the development of recommendations. Recently, guidelines related to specific interventions have included a table with

limited information on unit costs and estimated costs for a typical course of therapy. But relative cost effectiveness of options has generally not been considered. Although ASCO guidelines often recommend that clinicians and patients discuss issues of cost as a part of shared decision making, it is recognized that limited information may be available at the point of care about cost differences between drugs when third-party payers and negotiated prices are involved. Clinicians may also be guided by policies developed within their closed health care network or system.

Should specialty society–affiliated clinical practice guidelines serve as a mechanism for determining the relative value of treatment approaches, accounting for benefits, risks, and cost? Multidisciplinary guideline panels that form recommendations on the basis of systematic reviews of the literature in keeping with methods endorsed by the Institute of Medicine are in a good position to balance these tradeoffs and prioritize treatments relative to each other.

Nevertheless, there are myriad challenges to the conduct and interpretation of economic analyses in medicine. Cost is notoriously difficult to nail down in the US market. The cost of a drug may vary substantially between institutions and patients, depending on negotiations between various stakeholder parties. The standard metric for benchmarking drug prices in the United States, the average sales price plus 6%, does not reflect the true cost across contexts.

Moreover, there is a broader question of “cost to whom?”—that is, should the cost be considered from the perspective of patients, payers, government, or society as a whole? Prices change over time, particularly when market exclusivity expires and generic equivalents become available, therefore cost-effectiveness analyses become dated or obsolete as time passes. Guideline panels often lack adequate technical expertise to address these nuances. There may also be a cultural barrier to including such analyses: A concern among some clinicians

participating in guideline panels is that consideration of cost or relative economic value of treatments will distract from the scientific evidence focus of the guideline process and recommendations.

Despite these limitations and concerns, the time has come for clinical practice guidelines to include information about cost and relative economic value. Without such information, end users of guidelines will have incomplete information to inform appropriate decisions in the contemporary health care environment. Whenever available, high-quality economic analyses should be reviewed during guideline development. In addition, straightforward calculations assigning a known cost to a published unit of improvement (eg, incremental cost for one patient to attain an outcome of interest) can be conducted.

Standards are needed for interpreting and reporting economic analyses in ASCO guidelines. Ideally, this would include developing tools to assist end users in properly contextualizing recommendations within their particular economic setting. Wide variations in US pricing necessitate the development of aids for individual health care providers and patients to integrate information from guidelines into their specific settings, in order to appropriately estimate the relative value of treatments. Although an ASCO working group recommended integration of cost-effectiveness information into guidelines in 1995, this vision has yet to be operationalized.⁵ The working group noted that “all clinical practice guidelines, including ASCO’s, must be informed by cost-effectiveness considerations, or they risk being ignored.”^{5(p675)}

This issue of *Journal of Oncology Practice* includes a summary of the 2011 ASCO Antiemetic Guidelines Update.⁶ Authors of this commentary (E.B., G.L.) served as the panel chairs for this guideline. The guideline preferentially recommends palonosetron over other 5-HT₃ serotonin receptor antagonists for use with moderately emetogenic regimens. This recommendation is based on data suggesting an incremental clinical benefit for this agent. However, the cost of palonosetron is substantially greater than other drugs in its class. Although a basic cost table with average sales prices is included in the full version of the guideline at www.asco.org, based on current policies, there is no mention of the cost difference between agents in the recommendation itself. A statement is included in the recommendation that “if palonosetron is not available, clinicians may substitute a first generation 5-HT₃ serotonin receptor antagonist, preferably granisetron or ondansetron,”⁶ on the basis of an understanding that there may be site-specific constraints limiting access to palonosetron. The guideline panel did not explicitly review published cost-utility data regarding palonosetron or other agents in its class, although there are publications and health technology assessments in this area.⁷⁻⁹ Such information, if systematically reviewed, could be helpful both for guideline developers and end users.

Similarly, the guideline does not include quantitative details on the relative benefit of palonosetron compared with other 5-HT₃ serotonin receptor antagonists, or guidance on how to evaluate that added benefit relative to other care choices. Although such information is currently beyond the scope of ASCO guidelines, it might assist end users in evaluating alternative treatments and selecting one treatment or another within their individual settings. For example, a patient and his or her clinician would be better able to understand the relative benefits they are receiving by selecting a particular option and the additional cost associated with that choice. This may be particularly pertinent for patients facing substantial copays/out-of-pocket expenses. Although the ultimate choice of treatment would still be left to the patient and provider, that choice would be based on more specific and complete information from the guideline.

ASCO’s Clinical Practice Guideline Committee and Cost of Care Task Force have formed a working group to identify possible approaches to including cost and cost-effectiveness information in ASCO’s Clinical Practice guidelines. The goal of this effort is to provide information and tools for both guideline developers and end users, to enable informed decisions that account for real-world constraints while ensuring the highest quality of cancer care. Recommendations for evaluating and discussing relative value in future guidelines are anticipated for review and consideration by the ASCO Board of Directors.

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