

American Society of Clinical Oncology 2013 Top Five List in Oncology

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Processed as a Rapid Communication manuscript.

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Published online ahead of print at www.jco.org on October 29, 2013.

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

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0732-183X/13/3199-1/\$20.00

DOI: 10.1200/JCO.2013.53.3943

INTRODUCTION

The rising cost of health care continues to threaten the long-term vigor of the US economy. Cancer care, although a relatively small fraction of total US health care expenditures, is expected to increase from \$125 billion in 2010 to \$158 billion in 2020.¹ As a fractional change, this is comparable to the increase in total health care spending during the same period (\$4.8 trillion in 2021, up from \$2.6 trillion in 2010 and \$75 billion in 1970),² but nonetheless, it represents an important component of a problem that demands attention. As the leading medical professional oncology society committed to conquering cancer through research, education, prevention, and delivery of high-quality patient care, the American Society of Clinical Oncology (ASCO) has been actively engaged in initiatives to promote evidence-based decision making and more active engagement between physicians and their patients on the provision of high-value care. Our core belief is that physicians and patients, when participating in a system that supports evidence-based decision making and efficiency, will arrive at a course of action that optimizes health outcomes and value.

In 2012, ASCO participated in the Choosing Wisely Campaign, an initiative led by the American Board of Internal Medicine Foundation (ABIMF) to encourage conversations between physicians and patients about the overuse or misuse of medical tests and/or procedures that offer little benefit and may, in fact, be harmful. Led by the ASCO Value in Cancer Care Task Force (formerly Cost of Cancer Care Task Force), a top five list in oncology was published,³ garnering significant attention from the oncology community, media, and public at large. Since then, ASCO has devoted significant effort to educating physicians and patients about the Choosing Wisely initiative and driving practice change through the incorporation of the top five practices into the ASCO Quality Oncology Practice Initiative as a way to monitor their use. Evidence has subsequently emerged that practice changes—including new care models, recognition of the marginal utility

of some services, and wiser use of generic drugs—many of which are core to the Choosing Wisely Campaign, can continue to bend the medical cost curve in a favorable direction.^{4,5}

This year, ASCO was invited by ABIMF to contribute a second top five list (Table 1). As before, the goal was to identify commonly used tests, treatments, or other interventions of little or no benefit across the field of cancer medicine. To guide ASCO in this effort, suggestions were elicited from current ASCO committee members (approximately 700 individuals); 115 suggestions were received. After removing duplicates, researching the literature, and discussing practice patterns, the Value in Cancer Care Task Force culled the list to 11 items, which comprised an ASCO top five voting slate that was sent back to the membership of all standing committees. Approximately 140 oncologists from our leadership cadre voted, providing ASCO with an adequate sample size and perspective on what oncologists find to be of little value. The proposed 2013 top five list was reviewed and finalized by the Value in Cancer Care Task Force and ultimately reviewed and approved by the ASCO Board of Directors.

ASCO 2013 TOP FIVE LIST IN ONCOLOGY

1. Do not give patients starting a chemotherapy regimen that has a low or moderate risk of causing nausea or vomiting antiemetic drugs intended for use with a regimen that has a high risk of causing nausea or vomiting. Over the past several years, a large number of effective drugs with fewer adverse effects have been developed to prevent nausea and vomiting resulting from chemotherapy. When successful, these medications can help patients avoid spending time in the hospital, improve their quality of life, and lead to fewer changes in their chemotherapy regimen. Oncologists customarily use different antiemetic drugs depending on the likelihood (low, moderate, or high) of a particular chemotherapy program to cause nausea or vomiting. For chemotherapy programs that are almost certain to produce severe or persistent nausea or vomiting, there are new agents

Table 1. ASCO 2013 Top Five List in Oncology

Top Five List	Description
<p>Do not give patients starting a chemotherapy regimen that has a low or moderate risk of causing nausea or vomiting</p> <p>antiemetic drugs intended for use with a regimen that has a high risk of causing nausea or vomiting</p>	<p>Over the past several years, a large number of effective drugs with fewer side effects have been developed to prevent nausea and vomiting resulting from chemotherapy; when successful, these medications can help patients avoid spending time in the hospital, improve their quality of life, and lead to fewer changes in their chemotherapy regimen</p> <p>Oncologists customarily use different antiemetic drugs depending on the likelihood (low, moderate, or high) of a particular chemotherapy regimen to cause nausea or vomiting; for chemotherapy regimens that are almost certain to produce severe or persistent nausea or vomiting, there are new agents that can prevent this side effect; however, these drugs are expensive and have adverse effects; for this reason, these drugs should be used only when the chemotherapy drug has a high likelihood of causing severe or persistent nausea and vomiting</p> <p>When using chemotherapy that is less likely to cause nausea or vomiting, there are other effective drugs available at a lower cost.</p>
<p>Do not use combination chemotherapy (multiple drugs) instead of chemotherapy with one drug when treating an individual for metastatic breast cancer unless the patient needs a rapid response to relieve tumor-related symptoms</p>	<p>Although chemotherapy with multiple drugs (ie, combination chemotherapy) for metastatic breast cancer may slow tumor growth for a somewhat longer time than occurs when treating with a single drug, use of combination chemotherapy has not been shown to increase OS; in fact, the tradeoffs of more frequent and severe adverse effects may have a net effect of worsening a patient's quality of life, necessitating a reduction in the dose of chemotherapy</p> <p>Combination chemotherapy may be useful and worth the risk of more adverse effects in situations in which the cancer burden must be reduced quickly because it is causing significant symptoms or is life threatening; as a general rule, however, administering effective drugs one at a time lowers the risk of adverse effects, may improve a patient's quality of life, and does not typically compromise OS</p>
<p>Avoid using PET or PET-CT scanning as part of routine follow-up care to monitor for cancer recurrence in asymptomatic patients who have finished initial treatment to eliminate the cancer unless there is high-level evidence that such imaging will change the outcome</p>	<p>PET and PET-CT are used to diagnose, stage, and monitor how well treatment is working; available evidence from clinical studies suggests that using these tests to monitor for recurrence does not improve outcomes and therefore generally is not recommended for this purpose</p> <p>False-positive tests can lead to unnecessary and invasive procedures, overtreatment, unnecessary radiation exposure, and incorrect diagnoses</p> <p>Until high-level evidence demonstrates that routine surveillance with PET or PET-CT scans helps prolong life or promote well-being after treatment for a specific type of cancer, this practice should not be performed</p>
<p>Do not perform PSA testing for prostate cancer screening in men with no symptoms of the disease when they are expected to live fewer than 10 years</p>	<p>Because PSA levels in the blood have been linked with prostate cancer, many physicians have used repeated PSA tests in the hope of finding so-called early prostate cancer in men with no symptoms of the disease; unfortunately, PSA is not as useful for screening as many had hoped, because many men with prostate cancer do not have high PSA levels, and conditions other than cancer (eg, BPH) can also increase PSA levels</p> <p>Research has shown that men who receive PSA testing are less likely to die specifically as a result of prostate cancer; however, when accounting for deaths resulting from all causes, no lives are saved, meaning that men who receive PSA screening have not been shown to live longer than men who do not undergo PSA screening; men with medical conditions that limit their life expectancy to fewer than 10 years are unlikely to benefit from PSA screening, because their probability of dying as a result of the underlying medical problem is greater than the chance of dying as a result of asymptomatic prostate cancer</p>
<p>Do not use a targeted therapy intended for use against a specific genetic aberration unless a patient's tumor cells have a specific biomarker that predicts an effective response to the targeted therapy</p>	<p>Unlike chemotherapy, targeted therapy can significantly benefit people with cancer because it can target specific gene products (ie, proteins that cancer cells use to grow and spread) while causing little or no harm to healthy cells; patients who are most likely to benefit from targeted therapy are those who have a specific biomarker in their tumor cells that indicates the presence or absence of a specific gene alteration that makes the tumor cells susceptible to the targeted agent</p> <p>Compared with chemotherapy, the cost of targeted therapy is generally higher because these treatments are newer, more expensive to produce, and under patent protection; in addition, like all anticancer therapies, there are risks to using targeted agents when there is no evidence to support their use because of the potential for serious adverse effects or reduced efficacy compared with other treatment options</p>

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Abbreviations: ASCO, American Society of Clinical Oncology; BPH, benign prostatic hyperplasia; CT, computed tomography; OS, overall survival; PET, positron emission tomography; PSA, prostate-specific antigen.

that can prevent this adverse effect. However, these drugs are expensive and have adverse effects. For this reason, these drugs should be used only when the chemotherapy regimen has a high likelihood of causing severe or persistent nausea or vomiting. When using chemotherapy that is less likely to cause nausea or vomiting, there are other effective drugs available at a lower cost.

Nausea and vomiting remain among the most common, distressing, and yet treatable complications of systemic cancer chemotherapy. Several agents are available for reducing the risk and severity of chemotherapy-associated nausea and vomiting and are effective in the majority of patients. However, in patients receiving the most emetogenic chemotherapy agents and combination regimens, control of nausea and vomiting can be incomplete, leading to the recent introduction of more-effective but costly agents. Recent evidence-based guidelines from ASCO have partially reclassified the emetogenic classes of chemotherapeutic agents as well as defined the appropriate indications for these new agents in the care of patients with cancer.⁶ The updated guidelines reviewed optimal therapy for patients receiving highly emetogenic chemotherapy and the role of neurokinin 1 (NK₁) receptor antagonists in managing these symptoms. The potential role for recently introduced antiemetics in patients receiving high-dose chemotherapy with stem-cell support or in those receiving moderately emetogenic chemotherapy was also reviewed.

The systematic review made clear that for adults receiving highly emetogenic chemotherapy, the three-drug combination of an NK₁ receptor antagonist (days 1 to 3 for oral aprepitant; day 1 only for intravenous aprepitant), a 5-HT₃ receptor antagonist (day 1 only), and dexamethasone (days 1 to 3 or 1 to 4) is recommended. For patients receiving multiday chemotherapy, antiemetics appropriate for the emetic risk class of the chemotherapy should be administered each day on which chemotherapy is administered. As an example, for patients receiving 5-day cisplatin regimens, treatment with a 5-HT₃ antagonist in combination with dexamethasone and aprepitant is recommended. For those patients with persistent nausea or vomiting, the guidelines recommend that a continual reevaluation of emetic risk be performed to ascertain that the best regimen is being used.

For patients receiving moderately emetogenic agents, the two-drug combination of palonosetron (day 1 only) and dexamethasone (days 1 to 3) is recommended. If palonosetron is not available, clinicians may substitute a first-generation 5-HT₃ serotonin receptor antagonist, preferably granisetron or ondansetron. Both ASCO and National Comprehensive Cancer Network (NCCN) guidelines recommend palonosetron as the preferred agent based on an incremental benefit for this agent at providing protection against both nausea and vomiting in two large studies,^{7,8} although no significant difference was demonstrated in a third study.⁹ To accommodate site-specific constraints, and in view of the 10- to 100-fold greater cost associated with palonosetron,⁸ the guidelines state that if the drug is unavailable (or if its copay causes it to be unaffordable for the patient), clinicians may substitute a first-generation 5-HT₃ serotonin receptor antagonist, preferably granisetron or ondansetron.⁶

For patients receiving low emetogenic chemotherapy, a 5-HT₃ serotonin receptor antagonist is recommended, and for those experiencing nausea and vomiting while receiving radiation therapy, prophylactic use of these agents should continue until therapy has been completed.

At this time, neither ASCO nor NCCN guidelines explicitly consider cost in their recommendations. Such recommendations await

additional analyses that will include consideration of the cost of an agent along with valuation of its relative benefit. Because these assessments are not yet available, ASCO strongly advises oncologists to prescribe antiemetic agents in accordance with evidence-based guidelines and to avoid use of the costliest agents in situations in which less costly but equally effective drugs will control these toxicities. Patients whose nausea and vomiting are not adequately controlled despite receiving low or moderately emetogenic chemotherapy may, nevertheless, require more effective and costly agents.

2. *Do not use combination chemotherapy (multiple drugs) instead of chemotherapy with one drug when treating an individual for metastatic breast cancer unless the patient needs a rapid response to relieve tumor-related symptoms.* Although chemotherapy with multiple drugs (ie, combination chemotherapy) for metastatic breast cancer may slow tumor growth for a somewhat longer time than occurs when treating with a single drug, use of combination chemotherapy has not been shown to increase overall survival (OS). Combination chemotherapy may be useful and worth the risk of more adverse effects in situations in which the cancer burden must be reduced quickly because it is causing significant symptoms or is life threatening. As a general rule, however, administering effective drugs one at a time lowers the risk of adverse effects, may improve a patient's quality of life, allows for administration of maximum effective dose of each agent, allows assessment of the response to each agent, and does not typically compromise OS.

Cytotoxic chemotherapy for the treatment of life-threatening or recurrent breast cancer is one of the most potentially successful interventions available to oncologists. Commonly, patients experience a major degree of tumor regression after chemotherapy, which is often accompanied by palliation of their symptoms and may improve their progression-free survival (PFS). However, metastatic breast cancer remains an incurable illness with current antineoplastic therapies. Consequently, treatment of women with metastatic breast cancer must balance the benefit of the treatment with its adverse effects and the potential harm of the therapy. Judicious deployment of chemotherapy and management of its adverse effects must reflect our understanding of breast cancer as a chronic disease. Successful incorporation of chemotherapy into a comprehensive management strategy, which includes other cytoreductive and palliative treatment approaches discussed in this article, embodies both the science and the art of medical practice.

Combining multiple cytotoxic agents is clearly beneficial when chemotherapy is used as an adjunct to potentially curative breast surgery and radiation therapy. In this adjuvant setting, combination of two or more cytotoxic agents has demonstrably improved patient survival. The adjuvant setting is in stark contrast to that in metastatic breast cancer. In patients with advanced or metastatic cancer, the combination of two or more cytotoxic agents may provide higher rates of tumor response, more rapid tumor regression, and often a prolonged time to progression when compared with single-agent treatment. At the same time, combination chemotherapy is associated with heightened toxicity and an increased need for dose reduction. Furthermore, in most studies, an OS advantage with combination chemotherapy has not been demonstrated in patients with advanced disease. In treating metastatic disease, sequential single-agent therapy allows for the optimal delivery of each drug and reduces the risk of toxicity, an effect that may improve quality of life. Consequently,

combinations are usually reserved for treatment-naïve, highly symptomatic patients with visceral involvement, whose precarious situation requires a rapid tumor response.

Recent guidelines have addressed this issue. The First International Consensus Guidelines for Advanced Breast Cancer recommend “sequential monotherapy as the preferred choice” for metastatic breast cancer. This “strong recommendation” with “moderate quality evidence” states that “combination [chemotherapy] should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.”^{10(p247)} A Cochrane review of 43 informative clinical trials that included 9,742 women, 55% of whom were receiving their first treatment with chemotherapy for metastatic disease, concluded that “for women making a decision about treatment . . . this review was not able to address the issue of whether combination regimens are more effective than sequential treatment with different single agents.”^{11(p2)} NCCN guidelines are consistent, stating that “there is no compelling evidence that combination regimens are superior to sequential single agents,” with the level of evidence as 2A: “Based on lower level evidence, there is uniform consensus that the intervention is appropriate.”^{12(p1)} Note that these recommendations apply to the combination of cytotoxic chemotherapy agents. Combinations of biotherapeutic agents, such as anti-human epidermal growth factor receptor 2 therapy, with cytotoxic chemotherapy can improve survival compared with chemotherapy alone when the biomarker is present.^{13,14}

For hormone receptor–positive tumors, and in the absence of life-threatening organ dysfunction, serial endocrine therapies should be used before cytotoxic chemotherapy. New evidence suggests that even though resistance may develop to one member of a class of antihormone agents (eg, selective estrogen receptor modulators such as tamoxifen), tumor response may occur with another member of the class (eg, fulvestrant).¹⁵ All three of the metastatic breast cancer guidelines mentioned support this strategy. In the absence of life-threatening organ dysfunction, use of serial endocrine therapies is preferred for the treatment of estrogen receptor–positive tumors. Furthermore, there is generally no benefit to combining cytotoxic chemotherapy with an antihormonal agent.

It is important to note that neither single-agent nor combination chemotherapy should be the sole treatment modality employed in situations in which palliative radiation therapy or surgery may be more effective and less toxic. For painful bone metastases, especially if the cortex of weight-bearing bones is eroded and pathologic fracture imminent, short-course palliative radiation therapy should be considered.¹⁶ Palliative radiation therapy is also useful in preventing airway obstruction secondary to lung metastases or in symptomatic, unresectable CNS lesions. For abdominal metastases, when obstruction of hollow viscera occurs or is impending (eg, intestine, colon, or ureter), surgical resection, insertion of a stent, or radiation therapy may be more efficacious than initiating cytotoxic chemotherapy.

In summary, in a patient with advanced breast cancer who is not heavily pretreated and in whom symptomatic visceral crisis is apparent and rapid tumor response necessary, short courses of multiple-agent chemotherapy may be useful. However, as a general rule, administration of sequential single agents lowers the risk of adverse effects, may improve a patient’s quality of life, and does not typically compromise OS.

3. *Avoid using positron emission tomography or positron emission tomography–computed tomography scanning as part of routine follow-up care to monitor for cancer recurrence in asymptomatic patients who have finished initial treatment to eliminate the cancer unless there is high-level evidence that such imaging will change the outcome.* Positron emission tomography (PET) and PET–computed tomography (CT) are used to diagnose, stage, and monitor how well treatment is working. Available evidence from clinical studies suggests that using these tests to monitor for recurrence does not improve outcomes and therefore generally is not recommended for this purpose. False-positive tests can lead to unnecessary and invasive procedures, overtreatment, unnecessary radiation exposure, and incorrect diagnoses. Until high-level evidence demonstrates that routine surveillance with PET or PET-CT scans helps prolong life or promote well-being after treatment for a specific type of cancer, this practice should not be performed.

The ASCO initial top five list in oncology³ identified the use of PET or PET-CT for asymptomatic patients who have been treated for breast cancer with curative intent as a practice that is commonly performed, not supported by evidence, and therefore should be questioned. In the second ASCO list, we have broadened this recommendation to address the use of PET or PET-CT to monitor for recurrence in individuals with any cancer type treated with curative intent.

In the first few years after the approval of PET scanning for defined clinical indications, there was continual pressure on the Centers for Medicare and Medicaid Services (CMS) to expand indications and coverage. As a result of the CMS process of review, a number of indications for PET scanning have been supported. PET or PET-CT scanning has a high positive predictive value in many disease settings and can be particularly helpful in the evaluation and initial staging of disease. For example, the evidence level for its use in the evaluation of a solitary pulmonary nodule and initial staging of non–small-cell lung cancer is quite high, with acceptable cost-effectiveness parameters and even cost savings.^{17,18} Additional examples include staging and restaging of lymphoma, including Hodgkin lymphoma, evaluation of recurrence of melanoma before surgery, and determination of location of colon cancer metastases when carcinoembryonic antigen suggests recurrence. A particular concern, however, has been the potential overuse of PET-CT for surveillance of patients who have no evidence of disease after completion of therapy.

With the recent decision to end the National Oncology PET Registry, use of PET for routine surveillance is now clearly not recommended by CMS once staging and restaging is complete.¹⁹ An individual patient is covered for up to three PET scans for the rest of his or her life. The presumption is that PET will be used for staging and restaging of recurrence and not surveillance. CMS reviewed more than 50 recent studies for the final decision and could find no justification for PET scanning in surveillance. In concurrence with this assessment, Cancer Care Ontario systematically reviews the literature and to date has not recommended PET for surveillance.²⁰ ASCO, the European Union of Urology, the European Society for Medical Oncology,²¹ and NCCN have all declined to include surveillance PET in disease-specific guidelines.

A limitation in addressing the use of PET for follow-up while in remission is the absence of studies that are prospective, adequately powered, and measure outcomes of OS. Among the studies that have been published, Cheah et al²² analyzed 116 patients with diffuse large

B-cell lymphoma who underwent surveillance with PET-CT; 11 relapses were noted, seven of which were detected clinically. There was no evidence that early detection led to better survival. Zinzani et al²³ observed that of 30 positive PET studies in surveillance of primary mediastinal lymphoma (non-Hodgkin and Hodgkin lymphomas), 13 did not have relapsed lymphoma. A study by Evangelista et al²⁴ showed that PET used in 111 patients with breast cancer predicted the rate of relapse in 26 of 32 recurrences. However, there was no known survival benefit, and 48% of the results were false positives. In a prospective randomized trial of patients after curative liver resection for colon cancer, Sobhani et al²⁵ observed patients with PET. Use of PET was associated with a higher rate of second curative surgery. However, when other indicators of recurrence were excluded, there was no difference between PET and CT. Survival differences were unknown. Recent studies using a less costly technology (ie, CT) for surveillance have shown no improvement in survival in either non-Hodgkin or Hodgkin lymphoma, but have indicated an increase in the cost of care.^{26,27}

The utility of PET or PET-CT scanning for surveillance of both solid tumors and lymphomas remains unproven. In addition to clinical and economic considerations, the specter of unnecessary interventions and associated morbidity is a concern in the routine use of this technology for post-treatment surveillance.

4. Do not perform prostate-specific antigen testing for prostate cancer screening in men with no symptoms of the disease when they are expected to live fewer than 10 years. Because prostate-specific antigen (PSA) levels in the blood have been linked with prostate cancer, many physicians have used repeated PSA tests in the hope of finding so-called early prostate cancer in men with no symptoms of the disease. Unfortunately, PSA is not as useful for screening as many had hoped, because many men with prostate cancer do not have high PSA levels, and conditions other than cancer (eg, benign prostate hyperplasia [BPH]) can also increase PSA levels. Research has shown that men who receive PSA testing are less likely to die specifically as a result of prostate cancer. However, when accounting for deaths resulting from all causes, no lives are saved, meaning that men who receive PSA screening have not been shown to live longer than men who do not undergo PSA screening. Men with medical conditions that limit their life expectancy to fewer than 10 years are unlikely to benefit from PSA screening, because their probability of dying as a result of the underlying medical problem is greater than the chance of dying as a result of asymptomatic prostate cancer.

The introduction of the measurement of PSA into the algorithms for management of prostate cancer has been a mixed blessing.²⁸ PSA is a relatively specific protein that is associated with prostatic disorders, both benign and malignant, and generally correlates quite well with the existence of abnormalities of the prostate.²⁹ It is associated with BPH, and usually, the level increases to reflect the volume of BPH. PSA is also produced by malignant prostate tissues and often correlates with extent of disease as well as tumor progression. One of its limitations is that poorly differentiated prostate cancers often are PSA silent, or occasionally, there is a discrepancy between the volume or bulk of tumor and the amplitude of PSA production (with apparently modest levels of PSA suggesting the presence of lower tumor bulk than is actually present).

For years, the production of PSA from early-stage prostate cancer has been assessed in the hope that it would be useful as a screening tool to identify prostate cancer sufficiently early to allow routine curative

treatment.³⁰ It was reasoned that because screening allows early detection of many cancers and thus saves lives, early measurement of PSA should lead to early diagnosis of prostate cancer and thus the curative treatment of men with this disease. However, prostate cancer is a remarkably heterogeneous disease, and there clearly is a subtype that may exist in elderly men for many years that poses no threat to their longevity or lifestyle unless these are disrupted by the consequences of aggressive postscreening treatment.

Misinterpretation of early screening studies seemed to support the thought that community-based prostate cancer screening is useful. However, a series of randomized clinical trials has been reported, with follow-up in excess of 10 years, that dispute this notion. Some of these trials have shown a reduced number of deaths resulting from prostate cancer,³¹⁻³⁴ but there has been no evidence of lives saved overall. By contrast, in tumors for which screening techniques have been validated in randomized trials, OS (not only cause-specific survival) has been increased by screening. Furthermore, one randomized trial showed a deficit in survival in the screened population for older patients.³⁴

The US Preventive Services Task Force undertook a detailed analysis of all published data, with an emphasis on randomized clinical trials, and concluded that the use of serial measurement of PSA in asymptomatic men should not be used for population screening for prostate cancer because of the absence of real benefit and the possibility of harm to older patients.^{35,36} Subsequently, the American College of Physicians³⁷ reaffirmed a similar position. The American Urological Association has recently reversed its support of routine population screening and has proposed that only men age 55 to 69 years be considered for PSA screening.³⁸ ASCO has taken the position that patients with a life expectancy of fewer than 10 years should not be subjected to PSA screening, because the harms are likely to outweigh the benefits.³⁹ Of importance, none of the published series has had adequate numbers of African Americans or men with a positive family history (ie, populations at increased risk) to allow meaningful statements to be issued regarding screening in those two populations.

Web-based calculators to estimate the risk of a patient dying in the next 10 years are readily available and are based on well-designed, reliable studies. An example is EPrognosis (<http://eprognosis.ucsf.edu/>). A health care professional can rapidly and reliably estimate the chance of a person dying in the next years. What is clear is that we need to educate men about the existence of prostate cancer, its symptoms and presentations, the availability of treatment, and key facts related to the debate about screening.

5. Do not use a targeted therapy intended for use against a specific genetic aberration unless a patient's tumor cells have a specific biomarker that predicts an effective response to the targeted therapy. Unlike chemotherapy, targeted therapy can significantly benefit people with cancer because it can target specific gene products (ie, proteins that cancer cells use to grow and spread) while causing little or no harm to healthy cells. Patients who are most likely to benefit from targeted therapy are those who have a specific biomarker in their tumor cells that indicates the presence or absence of a specific gene alteration that makes the tumor cells susceptible to the targeted agent. Compared with chemotherapy, the cost of targeted therapy is generally higher because these treatments are newer, more expensive to produce, and under patent protection. In addition, like all anticancer therapies, there are risks to using targeted agents when there is no evidence to support their use

because of the potential for serious adverse effects or reduced efficacy compared with other treatment options.

The concept of targeted therapy for cancer was born after the recognition that chronic myeloid leukemia is driven by a unique oncoprotein with tyrosine kinase properties and the introduction of imatinib as a potent inhibitor of this kinase that could produce rapid and sustained remissions in the majority of patients with this disease.^{40,41} Cancer drug development has since veered away from a focus on broad-spectrum, nonspecific cytotoxic drugs to development of agents that specifically interrupt oncogenic molecular pathways that are often driven by mutation, overexpression, or translocation of specific genes. In many cases, specific tests have been developed to identify abnormalities in tumor cells such as a biomarker of susceptibility or resistance to treatment with a targeted agent. Use of these tests has facilitated more rapid development of targeted therapies for cancer, and many drug development programs now select patients for participation in clinical trials based on the presence or absence of a specific biomarker, often a specific genetic mutation, in the tumor. Successful agents are then typically approved for use in patients whose tumors harbor the targeted genetic aberration, detected with a well-validated test. In clinical practice, physicians use such test results to identify patients for treatment with the drug. This new paradigm in cancer drug development has led to the recent introduction of a number of novel agents best exemplified by the US Food and Drug Administration approval of crizotinib for treatment of non–small-cell lung cancer harboring an *EML4-ALK* translocation⁴²; afatinib for treatment of metastatic non–small-cell lung cancer harboring specific epidermal growth factor receptor (*EGFR*) gene mutations⁴³; and vemurafenib, dabrafenib, and trametinib^{44,45} for treatment of melanoma with *BRAF* V600E or V600K mutations. The limitations of this approach are also becoming well known and include the lack of validated predictive biomarkers for many targeted agents, the observation of clinical activity of a drug even in some biomarker-negative cases, and the rapid emergence of resistance to most targeted therapies.

In some cases, development of predictive biomarkers has lagged behind the introduction of drugs and new information obtained from postmarketing studies and has then been incorporated into clinical guidelines or revised product labels to provide guidance to physicians and patients on optimal use of a drug. Perhaps the best example is the recognition that certain mutations in the *EGFR* gene confer sensitivity to small-molecule tyrosine kinase inhibitors (TKIs) only after the introduction of gefitinib and erlotinib into (and in the case of gefitinib, after the withdrawal from) clinical practice.⁴⁶ Erlotinib thus remains labeled for use in patients with advanced (second- or third-line treatment of metastatic disease) non–small-cell lung cancer based on clinical trials that demonstrated a modest survival benefit compared with best supportive care in an unselected population, even though current information suggests that the drug effect is greatest in those tumors harboring a sensitizing *EGFR* mutation.⁴⁷ Indeed, when the drug is contemplated for use as first-line treatment for patients with metastatic disease, an ASCO provisional clinical opinion now recommends testing of tumors for *EGFR* mutations to determine whether TKI treatment or chemotherapy is the most appropriate approach,⁴⁸ and a recent revision to the erlotinib label now extends its use to first-line treatment of metastatic non–small-cell lung cancer harboring an *EGFR* gene mutation. Information obtained from postmarketing studies was also used to modify the use of the anti-*EGFR* monoclonal antibodies cetuximab and pani-

tumumab for treatment of patients with metastatic colorectal cancer. Initial clinical trials demonstrated a modest improvement in OS compared with best supportive care when patients with metastatic colorectal cancer received treatment with these agents.^{49,50} After their approval and marketing, new information became available that demonstrated no clinical benefit from these drugs in patients with colorectal cancers harboring certain mutations in the *KRAS* gene.^{50,51} ASCO published a provisional clinical opinion recommending against the use of these agents for treatment of tumors harboring mutations at codons 12 or 13 in the *KRAS* gene,⁵² and the drug sponsors, working with the US Food and Drug Administration, revised the drug labels to indicate that the drugs should be used only for treatment of tumors with *KRAS* wild-type genes.

These examples provide the underpinning of the ASCO recommendation that agents intended for use against a specific genetic target not be used unless a specific biomarker is present in the patient's tumor cells that predicts for effectiveness of the targeted therapy. As agents recently introduced into the marketplace, many targeted therapies are far more expensive than other possible therapeutic options. Although often considered relatively nontoxic, many targeted agents carry a risk of significant adverse effects that can negatively affect patients' quality of life, such as fatigue, rash, diarrhea, allergic reaction, electrolyte disturbance, hypothyroidism, hypertension, and even treatment-related malignancy. In some cases, selection of a targeted agent in place of other options for treatment of patients with a biomarker-negative tumor produces adverse treatment outcomes. This has now been well documented in the treatment of patients with non–small-cell lung cancer with *EGFR* TKIs, where survival is worse than that achieved with cytotoxic chemotherapy when a TKI is used in treatment of patients whose tumors do not have a sensitizing *EGFR* mutation.⁵³ Similarly, panitumumab or cetuximab used in combination with chemotherapy for treatment of advanced colorectal cancer produces improved PFS in patients with *KRAS* wild-type tumors but worse PFS in those with *KRAS*-mutant tumors.^{54,55}

The selection and use of targeted agents for cancer treatment should be guided by the unique clinical circumstances of each patient and the strength of the clinical evidence that supports each treatment option. In some cases, targeted therapies are indicated for use only when a patient's tumor harbors a specific genetic aberration that is detected with an analytically validated test either because the drug has not been tested in biomarker-negative cases or because it has been tested and proven ineffective in such cases. In other circumstances, a targeted therapy might have the greatest chance for benefit when a predictive biomarker is detected in the tumor but might still confer some benefit even in biomarker-negative cases. This might occur when the standard test fails to detect all drug-sensitive variants of the target; when the drug inhibits multiple targets, not all of which are detectable with the approved test; or when inhibition of the targeted pathway inhibits tumor growth even in the absence of mutation-driven pathway hyperactivity.

However, as a general principle, ASCO recommends against the use of targeted agents intended for use in patients whose tumors harbor a specific genetic aberration unless the patient's tumor has been tested with a validated test and demonstrated to have a drug-sensitive variant of that aberration. An exception to this can occur if high-level evidence supports use of the targeted agent despite absence

of the biomarker. Conversely, if a mutational analysis demonstrates a mutation in a gene not usually associated with the tumor type in question, an available targeted therapy ought not be used outside of a clinical trial unless there is no therapeutic alternative and evidence supports its utility in that context.

DISCUSSION

The items discussed in the ASCO 2013 Top Five List address five interventions that are frequently used in the management of common problems in clinical oncology. As was the case with the 2012 publication of the first ASCO top five list,³ our primary purpose is to enhance patient care by encouraging proper use of diagnostic and treatment modalities, avoiding overuse or misuse, and stimulating discussions about these subjects between physicians and their patients. Inappropriate use of screening or diagnostic tests carries the risk of discomfort or danger as well as excess morbidity. Furthermore, misuse and overuse contribute to a vast increase in the cost of health care and add financial burdens for our patients (via premium increases and copays) as well as for the economy as a whole.

The issue of antiemetics, in particular, has received significant scrutiny over the last several years. New antiemetics have had a positive impact on patients' tolerance of highly emetogenic chemotherapy. This progress brings with it the high costs of these novel agents, an effect that amplifies the financial impact of delivering chemotherapy. When used in patients treated with highly emetogenic agents, these medications can reduce morbidity and help patients stay on their prescribed treatment schedule; they are thus strongly preferred. However, when using chemotherapy that is less likely to cause nausea or vomiting, agents recommended for use with highly emetogenic chemotherapy should be avoided if equally effective drugs are available at lower cost. ASCO is encouraging adherence to guidelines for antiemetic use that match the level of emetogenicity associated with a specific treatment regimen.

Combination chemotherapy has been curative in a number of advanced disease settings such as testicular carcinoma, large B-cell non-Hodgkin lymphoma, Hodgkin lymphoma, Burkitt's lymphoma, and acute leukemias. However, in metastatic breast cancer, combining active single agents has not had a major impact in the disease. Despite attempts at increasing the dose and dose-intensity of combinations, cure has not been possible. In the absence of an OS advantage in most studies that have addressed this issue, it is appropriate to confine the use of combination chemotherapy in metastatic breast cancer to the clinical trial setting or to clinical situations characterized by life-threatening visceral involvement or an urgent need for palliation of tumor-related symptoms. Doing so will optimize patients' quality of life by minimizing toxicity, facilitate palliation to the extent possible by the single agent employed, and have the corollary effect of reducing expenses through fewer hospitalizations, less need for growth factor support, and use of regimens that are likely to be lower in cost.

The next two items of the ASCO 2013 top five list address the use or misuse of technologies to screen or detect the presence of disease at its earliest state. Use of PET or PET-CT scanning to monitor for recurrence in patients treated with curative intent has not been proven to change patient outcome. Simply put, for most diseases for which primary treatment and appropriate restaging has been completed, there is no evidence that detection of preclinical relapse through sur-

veillance PET or PET-CT scanning improves outcomes through the introduction of salvage therapy in the context of a smaller burden of disease. The available evidence supports the contention that most recurrences of diseases for which curative salvage therapy is available (eg, large B-cell non-Hodgkin lymphoma) are usually discovered through clinical examination or laboratory studies, not imaging. In the absence of evidence supporting the lifesaving potential of costly imaging technologies, they should not be used. In fact, not using them avoids the possibility of false-positive results, which engender the subsequent risk of interventional biopsies or unnecessary surgical procedures, with the associated risks to the patient and heightened anxiety.

The issue of PSA testing for prostate cancer screening has been hotly debated over the last few years. Although the concept of identifying early prostate cancer in asymptomatic older men is attractive, to date, its use has not resulted in a net saving of lives. With PSA testing, we are unable to reliably distinguish the more dangerous cancers from those that are relatively innocuous. This is the case in older men, many of whom have a limited lifespan and in whom prostate cancer is likely to be either an indolent disease requiring little or no treatment or a chronic, protracted disease that will not cause an excess of premature deaths. Thus, it is the opinion of ASCO that screening with the PSA test in men with a life expectancy shorter than 10 years not be done and that by not doing so, men will be spared the morbidity of a diagnosis that need not have been made and unnecessary treatment.

Finally, targeted therapies hold the promise of individualizing each patient's treatment based on the unique molecular features of his or her tumor. Increasingly, research has demonstrated that biomarkers can be used to select patients most likely to benefit from certain treatments. In some cases, targeted therapies are indicated for use only when a patient's tumor harbors a specific genetic aberration either because the drug has not been tested in biomarker-negative cases or because it has been tested and proven ineffective in such cases. In other circumstances, a targeted therapy may have the greatest chance for benefit when a predictive biomarker is detected in the tumor but might still confer some benefit even in biomarker-negative cases. In some cases, selection of a targeted agent in place of other options for treatment of patients with biomarker-negative tumors produces adverse treatment outcomes. Although often considered relatively non-toxic, many targeted agents carry a risk of significant adverse effects that can adversely affect patients' quality of life. Moreover, the financial toxicity to both the patient and the health care system attributable to the enormous cost of a drug being sold under patent protection is also an important consideration.

ASCO's advocacy for a second top five list is recognition of its commitment to the highest standards of care for patients with cancer. This translates to a mandate to the clinical oncologist to prescribe the right care in the right amount, employing the right techniques, at the right time. The fruits of these efforts will be delivery of the highest value of cancer care that is supported by scientific evidence. Simultaneously, ASCO recognizes that the science and art of medicine are based on honoring the individuality of each of our patients. Hence, the items on the list are meant as evidence-based advisories to our colleagues in clinical oncology, with the suggestion that the recommendations represent an opportunity for in-depth discussions with the patient and individualized treatment planning.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Lowell E. Schnipper, Up to Date (C); J. Russell Hoverman, Texas Oncology (C), US Oncology (C)
Consultant or Advisory Role: Lowell E. Schnipper, evite (C); Douglas W. Blayney, Clinical Oncology Advisory Group (C), Michigan Oncology Quality Consortium (C), Oregon Health Sciences University Knight-Legacy Collaboration (C), California HealthCare Foundation (C), Physician Resource Management (C); J. Russell Hoverman, United

HealthCare (C); Derek Raghavan, Gerson Lehrman Group (C), sanofi-aventis (U) **Stock Ownership:** Douglas W. Blayney, Abbot Laboratories, Amgen, Bristol-Myers Squibb, Covidien, Express Scripts, Johnson & Johnson, Mallinckrodt, United Healthcare **Honoraria:** Douglas W. Blayney, Cancer Centers of Excellence **Research Funding:** Douglas W. Blayney, Blue Cross Blue Shield of Michigan **Expert Testimony:** None **Patents:** None **Other Remuneration:** None

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Final approval of manuscript: All authors

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Appendix

The American Society of Clinical Oncology (ASCO) 2013 top five list in oncology was reviewed and transmitted to the ASCO Board of Directors by the ASCO Value in Cancer Care Task Force: Lowell E. Schnipper, MD, chair (Beth Israel Deaconess Medical Center, Boston, MA); Joseph Bailes, MD (ASCO, Alexandria, VA); Douglas W. Blayney, MD (Stanford University School of Medicine, Stanford, CA); Diane Blum, MSW (Lymphoma Research Foundation, New York, NY); Nancy Davidson, MD (University of Pittsburgh Cancer Institute and University of Pittsburgh Medical Center Cancer Centers, Pittsburgh, PA); Patricia Ganz, MD (University of California, Los Angeles, Schools of Medicine and Public Health, Los Angeles, CA); J. Russell Hoverman, MD, PhD (Texas Oncology, Dallas, TX); Robert Langdon, MD (Nebraska Cancer Specialists, The Physicians of Oncology Hematology West, Omaha, NE); Allen Lichter, MD (ASCO, Alexandria, VA); Gary H. Lyman, MD (Duke University, Durham, NC); Neal J. Meropol, MD (Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH); Therese Mulvey, MD (Southcoast Center for Cancer Care, Southcoast Health System, Fairhaven, MA); Lee Newcomer, MD (United Healthcare, Edina, MN); Blase Polite, MD, MPH (University of Chicago Medical Center, Chicago, IL); Jeffrey Peppercorn, MD, MPH (Duke University, Durham, NC); Derek Raghavan, MD, PhD (Levine Cancer Institute, Carolinas HealthCare, Charlotte, NC); Gregory Rossi, PhD (AstraZeneca, Macclesfield, United Kingdom); Deborah Schrag, MD (Dana-Farber Cancer Institute, Boston, MA); Richard Schilsky, MD (ASCO, Alexandria, VA); and Thomas J. Smith, MD (Sidney Kimmel Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD).