Managing the Financial Impact of Cancer Treatment: The Role of Clinical Practice Guidelines

Scott Ramsey, MD, PhD, and Veena Shankaran, MD

The rising cost of cancer treatment in the United States poses a significant challenge to health systems, government and private insurers, and individual patients. To some degree, cancer treatment costs are rising due to inappropriate, non–evidence-based use of expensive new technologies and drugs. However, adherence to evidence-based clinical practice guidelines does not necessarily guarantee that cancer treatment will be less costly or optimally cost-effective. Although clinical practice guidelines may endorse many acceptable evidence-based treatment options, the financial implications of different treatment decisions within these guidelines can vary significantly. In the case of first-line treatment for metastatic colorectal cancer (CRC) and gastric cancer, for example, the cost of 6 months’ treatment varies widely while the clinical effectiveness of these regimens is comparable. Patients’ out-of-pocket payments for various treatment regimens may also vary significantly. In the setting of rapidly rising cancer treatment costs, it is essential that clinical practice guidelines begin to incorporate economic information from the patient and health system perspectives to minimize the financial impact of cancer care on patients and society.

The Influence of Clinical Practice Guidelines

Clinical practice guidelines play a vital role in providing oncologists and patients with evidence-based cancer treatment algorithms. Clinical practice guidelines also broadly influence what patients, health delivery systems, and health insurers pay for cancer care. The economic impact of treatment decision-making on these stakeholders has been of great interest recently.

Patients are increasingly faced with high copayments and other treatment-related expenses, which may not only cause significant anxiety but also may limit their ability to pay for basic necessities such as food and housing.1 In a recent population-based survey of patients with CRC receiving adjuvant chemotherapy, 38% experienced severe financial hardship (defined as accruing debt, borrowing money from friends or family, selling/refinancing their primary home, or ≥ 20% decline in income).2 From a societal standpoint, cancer treatment costs in the United States are projected to increase by as much as 39% by 2020.3 Although efforts to discourage the use of non–evidence-based procedures, tests, and treatments may help curb these rising costs to some degree, the high variability in the costs of evidence-based treatments remains an economic challenge for patients and other key stakeholders.4–6 Reducing the financial burden of cancer treatment while maintaining high-quality care will require a coordinated national strategy. In this commentary, we argue that oncology clinical practice guidelines have a key role in this national effort.

Current Role of Clinical Practice Guidelines

Clinical practice guidelines are intended primarily to summarize scientific evidence, formulate best practice recommendations, and reduce variations in care. Practice guidelines in oncology reflect the opinion of expert clinicians regarding single or multiple evidence-based approaches to treating an individual with cancer. Selecting among the range of acceptable treatment options depends on clinical assessment of characteristics, such as performance status, medical comorbidity, and prior treatment.

The ideas and viewpoints expressed in this editorial are those of the author and do not necessarily represent any policy, position, or program of NCCN.
Most oncology guidelines do not explicitly incorporate nonclinical factors, such as treatment cost, expected patient out-of-pocket financial burden, or cost-effectiveness, into the guideline development process.

Public and private health insurers commonly use guidelines and compendia to support reimbursement decisions. The NCCN Drugs & Biologics Compendium, for example, is recognized by the Centers for Medicare and Medicaid Services (CMS) and UnitedHealthcare as a standard reference for oncology coverage policy.\(^7\)

Choosing Between Multiple Guideline-Supported Treatment Options

In addition to clinical factors such as performance status and medical comorbidity, other patient characteristics may influence selection of a particular treatment regimen from a range of acceptable options. Characteristics such as distance to infusion center and convenience (eg, pills vs. infusion) may also influence decisions. These factors are not routinely addressed in clinical practice guidelines, but patients and physicians can usually sort out how these issues might factor into the treatment plan.

However, the potential financial impact of treatment choices on patients, health systems, and health insurers can be difficult to predict. Patients and physicians often have very little advance knowledge about copayments for chemotherapeutics or supportive medications. Further, many oncologists in the United States do not know the differential total costs associated with one chemotherapy regimen versus another.\(^8\)

Clinical guidelines list a number of “acceptable” treatment options, but rarely address the financial variability of those options. Given the rising cost of cancer care, we believe that physicians and patients need to understand the financial implications of their treatment decisions. The next question, however, is whether guidelines can—and should—report expected financial outcomes for regimens considered to be therapeutically acceptable based on clinical evidence.

Examples: Variability in CRC and Gastric Cancer Treatment Recommendations

Clinical practice guidelines that support several evidence-based treatment options without reference to cost may result in very different financial outcomes for insurers, health systems, and patients. We present 2 examples of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for first-line therapy in metastatic cancer to illustrate this issue.

Metastatic CRC

Several first-line treatment options exist for patients with good performance status who can tolerate intensive therapy. Some of these options depend on KRAS mutational status, which has been shown to predict responsiveness to the anti–epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab.\(^9,10\) Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has also been shown to improve survival in the first-line treatment setting.\(^11\) Many of the first-line CRC regimens endorsed in the NCCN Guidelines are outlined in Table 1.\(^12\)

Although median survival is relatively comparable between regimens (range, 21.3–28.0 months), Medicare reimbursement rates vary significantly from one regimen to the next (range, $2200–$10,000 per treatment cycle). Patients with metastatic CRC may receive multiple regimens over time (Table 1), potentially minimizing cost savings seen with the first regimen; however, the treatment duration may also be...
combinations. For patients with excellent performance status, the NCCN Guidelines endorse multiple 3-drug combinations. In a first-line gastric cancer clinical trial that used a 2 x 2 factorial design to compare 4 different triple-drug regimens, all regimens were associated with comparable response and median survival rates, but toxicity profiles varied. As in the previous example for longest with the first regimen. Thus, the financial impact of this initial decision is significant.

**Metastatic Gastric Cancer**

For patients with metastatic gastric cancer, several first-line treatment options supported by the NCCN Guidelines are available, ranging from single drugs to 3-drug combinations. For patients with KRAS wild-type only.

### Table 1 First-Line Combination Regimens in the NCCN Guidelines for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Initial Regimen and Study</th>
<th>Regimen and Dosing Schedule</th>
<th>Median OS</th>
<th>Medicare Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 Cycle*</td>
</tr>
<tr>
<td>mFOLFOX6 + bevacizumab13,14</td>
<td>Every 14 days: Oxaliplatin, 85 mg/m² IV, day 1 Leucovorin, 400 mg/m² IV, day 1 S-FU, 400 mg/m² IV bolus, day 1 S-FU, 1200 mg/m²/day CIV, days 1 and 2 Bevacizumab, 5 mg/kg, day 1</td>
<td>21.3 mo</td>
<td>$5005.42</td>
</tr>
<tr>
<td>CapeOx + bevacizumab15-17</td>
<td>Every 21 days: Oxaliplatin, 130 mg/m² IV, day 1 Capecitabine, 850–1000 mg/m² PO bid, days 1–14 Bevacizumab, 7.5 mg/kg, day 1</td>
<td>21.3 mo</td>
<td>$10,077.15</td>
</tr>
<tr>
<td>FOLFIRI + bevacizumab17,18</td>
<td>Every 14 days: Irinotecan, 180 mg/m² IV, day 1 Leucovorin, 400 mg/m² IV, day 1 S-FU, 400 mg/m² IV bolus, day 1 S-FU, 1200 mg/m²/day CIV, days 1 and 2 Bevacizumab, 5 mg/kg IV, day 1</td>
<td>28.0 mo</td>
<td>$2247.60</td>
</tr>
<tr>
<td>mFOLFOX6 + panitumumab10,b</td>
<td>Every 14 days: Oxaliplatin, 85 mg/m² IV, day 1 Leucovorin, 400 mg/m² IV, day 1 S-FU, 400 mg/m² IV bolus, day 1 S-FU, 1200 mg/m²/day CIV, days 1 and 2 Panitumumab, 6 mg/kg, day 1</td>
<td>23.9 mo</td>
<td>$6534.97</td>
</tr>
<tr>
<td>FOLFIRI + cetuximab5,19,b</td>
<td>Every 14 days (cetuximab either every 7 or 14 days): Oxaliplatin, 85 mg/m² IV, day 1 Leucovorin, 400 mg/m² IV, day 1 S-FU, 400 mg/m² IV bolus, day 1 S-FU, 1200 mg/m²/day CIV, days 1 and 2 Panitumumab, 6 mg/kg, day 1</td>
<td>23.5 mo</td>
<td>$4399.62</td>
</tr>
<tr>
<td>FOLFIRI + panitumumab</td>
<td>Every 14 days: Oxaliplatin, 165 mg/m² IV, day 1 Leucovorin, 400 mg/m² IV, day 1 S-FU, 400 mg/m² IV bolus, day 1 S-FU, 1200 mg/m²/day CIV, days 1 and 2 Panitumumab, 6 mg/kg, day 1</td>
<td>NA</td>
<td>$3777.11</td>
</tr>
<tr>
<td>FOLFOXIRI20</td>
<td>Every 14 days: Oxaliplatin, 165 mg/m² IV, day 1 Leucovorin, 400 mg/m² IV, day 1 S-FU, 1600 mg/m²/day CIV, days 1 and 2 Panitumumab, 6 mg/kg, day 1</td>
<td>22.6 mo</td>
<td>$2910.77</td>
</tr>
</tbody>
</table>

Abbreviations: BSA, body surface area; CIV, continuous intravenous infusion; IV, intravenous; OS, overall survival; PO, orally.

aMedicare reimbursement rate based on 2012 average sale price; dosing calculations based on weight 70 kg and BSA 1.7 m²
bFor patients with KRAS wild-type only.

cIn the cited clinical trials, panitumumab was combined with FOLFOX4; however, NCCN Guidelines list mFOLFOX6 + panitumumab as a first-line treatment option.
benefit rather than an outpatient prescription, many patients with commercial insurance might experience very high copayments for oral chemotherapeutics, including capecitabine. Under some insurance plans with tiered formularies, these copayments may be as high as 50% of the total monthly cost for the drug. The variability in patient prescription plans and drug coverage policies for oral chemotherapeutics can profoundly impact a patient’s treatment-related financial experience. Further, the out-of-pocket expenses associated with a new regimen are difficult to predict, making preemptive conversations about anticipated costs difficult.

Ignoring Nonclinical Issues Reduces the Potential Impact of Practice Guidelines

The costs of chemotherapy regimens commonly used in metastatic CRC and gastric cancer vary greatly. Practice guidelines that give equal weight to these regimens create a situation in which accepted variations may produce vastly different economic outcomes for patients and society while producing potentially equivalent clinical outcomes. In particular, high out-of-pocket expenses associated with oral chemotherapeutics can result in nonadherence and, in turn, poorer response

### Table 2 Triple-Drug First-Line Systemic Chemotherapy Options for Metastatic Gastric Cancer in the NCCN Guidelines

<table>
<thead>
<tr>
<th>Initial Regimen and Study</th>
<th>Regimen and Dosing Schedule</th>
<th>Median OS, (m)</th>
<th>Medicare Reimbursement 1 Cycle</th>
<th>Medicare Reimbursement 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCF&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Every 28 days:</td>
<td>9.2</td>
<td>$1534.43</td>
<td>$9206.56</td>
</tr>
<tr>
<td></td>
<td>Docetaxel, 75 mg/m² IV, day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin, 75 mg/m² IV, day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-FU, 1000 mg/m²/day CIV, days 1–5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECF&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Every 21 days:</td>
<td>9.9</td>
<td>$104.98</td>
<td>$839.84</td>
</tr>
<tr>
<td></td>
<td>Epirubicin, 50 mg/m² IV, day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin, 60 mg/m² IV, day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-FU, 200 mg/m²/day CIV, days 1–21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECX&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Every 21 days:</td>
<td>9.9</td>
<td>$2269.06</td>
<td>$18,152.51</td>
</tr>
<tr>
<td></td>
<td>Epirubicin, 50 mg/m² IV, day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin, 60 mg/m² IV, day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capecitabine, 625 mg/m² PO bid, days 1–21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EOF&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Every 21 days:</td>
<td>9.3</td>
<td>$4420.67</td>
<td>$35,365.32</td>
</tr>
<tr>
<td></td>
<td>Epirubicin, 50 mg/m² IV, day 1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin, 130 mg/m² IV, day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-FU, 200 mg/m² CIV, days 1–21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EOX&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Every 21 days:</td>
<td>11.2</td>
<td>$7184.75</td>
<td>$57,478.03</td>
</tr>
<tr>
<td></td>
<td>Epirubicin, 50 mg/m² IV, day 1</td>
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</tr>
<tr>
<td></td>
<td>Oxaliplatin, 130 mg/m² IV, day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capecitabine, 625 mg/m² PO bid, days 1–21</td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: BSA, body surface area; CIV, continuous intravenous infusion; IV, intravenous; OS, overall survival; PO, orally.

*Dosing calculations based on weight of 70 kg and BSA of 1.7 m².*

*Medicare reimbursement rate based on 2012 average sale price; dosing calculations based on weight of 70 kg and BSA of 1.7 m².*

metastatic CRC, the cost associated with one treatment cycle varies widely among regimens (range $100–$7000; Table 2). Because many patients with gastric cancer do not reach second- or third-line therapy, choice of first-line treatment can have a dramatic impact on overall costs associated with treatment.

### Out-of-Pocket Expenses

Importantly, the out-of-pocket expenses associated with particular chemotherapy regimens can vary widely depending on the patient’s insurance plan and state of residence. A Medicare patient without a supplemental insurance plan, for example, may be responsible for 20% of the costs of all chemotherapeutics (infusional and capecitabine), whereas a patient with a supplemental plan may have complete coverage for these drugs. Although capecitabine is covered under Medicare Part B, many other oral chemotherapeutics used in other diseases (eg, sunitinib and erlotinib) are covered under Medicare Part D, which means that patients receiving these drugs often reach the $4700 out-of-pocket “donut hole” in coverage very early on in their treatment course.

Except in certain states that have legislation requiring that oral chemotherapeutics be covered as a medical

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rates or survival. Providers must be aware of the impact that high out-of-pocket costs have on their patients.23,24

A Way Forward: Acknowledging Economic Issues in Practice Guidelines

We believe it is crucial that the oncology community take the lead in encouraging cost-effective prescribing practices and developing supplementary information that allows clinicians and patients to understand the personal financial consequences of specific therapeutic options. Below, we describe 4 items that could be incorporated into clinical practice guidelines today to move toward this goal:

• Identify a minimal clinical difference among therapeutic choices and group therapies that are equivalent within that range.
• Identify the lowest cost option to patients within a group of acceptable alternatives, based on minimal clinical differences.
• Provide information to oncologists and patients on the expected total costs and personal financial costs of recommended regimens.
• Develop practice guidelines language that allows health insurers to promote care that minimizes financial burden to patients and health systems.

We acknowledge that these recommendations create additional burdens for organizations that produce clinical practice guidelines. Obtaining information on expected patient out-of-pocket and total costs requires surveying health insurers and tracking current drug prices. These tasks are not impossible, however. With the possible exception of drugs included in Part D, Medicare coverage policies are fairly uniform nationally, making it a relatively straightforward task to estimate patient copayments and deductibles for common regimens. Medicare’s Web site also provides some information to help patients understand their potential out-of-pocket expenses (www.medicare.gov).

Coverage policies among commercial insurance plans contain more variability, but regular surveys of the most common oncology drug policies in the largest plans could provide valuable data. In addition, many drug manufacturers now produce budget impact analyses of their products and share these with insurance plans that request them. Guidelines groups could similarly request these analyses to inform the guideline development process.

Conclusions

Any treatment decision in oncology, even those based on strong clinical evidence, can have major financial impacts on patients, insurers, and society. Particularly in situations where many evidence-based treatment options exist, clinicians have tremendous influence over the cost of cancer treatment. Moving forward, incorporation of cost information into guidelines development will help increase awareness of the economic implications of routine clinical decision-making and reduce the financial burden of cancer treatment on patients and society.

References


