Response

We agree with Cohen and Looney about the need for “a more systematic and better coordinated evidence base . . . for both labeled and off-label use of oncology therapeutics to provide information for prescribing and reimbursement decisions.” It is our belief that continued development of such evidence should be guided by thoughtful deliberation about the goals and benefits of prescribing particular cancer therapies, as well as consideration of their costs. As for other comments, in the spirit of a collegial discourse, we offer the following reply to their criticisms of our recommendations.

They begin by arguing, without providing examples, that “surely some cancer drugs with cost per QALY ratios of more than $129 000 are worth prescribing to treat a previously incurable condition or to alleviate suffering” (where QALY is quality-adjusted life-years). However, as we thought
Table 1. Estimates of drug costs according to quality-adjusted life-years (QALYs)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease, first author, year (reference)</th>
<th>Regimen</th>
<th>Dose†</th>
<th>PFS or time on therapy‡</th>
<th>Amount needed§</th>
<th>Cost per milligram or cost per tablet</th>
<th>Total cost §</th>
<th>Increase in OS,</th>
<th></th>
<th>mo</th>
<th>Cost per QALY¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>NSCLC, Reck, 2009 (2)</td>
<td>15 mg/kg every 21 d</td>
<td>900 mg every 21 d</td>
<td>5 cycles†</td>
<td>4500 mg</td>
<td>$6.70 per mg</td>
<td>$30,150</td>
<td>0.3†</td>
<td>$1,206,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>Pancreatic cancer, Moore, 2007 (1)</td>
<td>150 mg daily</td>
<td>150 mg/d or 1 tablet per day</td>
<td>3.75 mo*</td>
<td>114 tablets</td>
<td>$160.76 per tablet</td>
<td>$18,327</td>
<td>0.33</td>
<td>$659,772</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Breast cancer, Miller, 2007 (3)</td>
<td>10 mg/kg every 14 d</td>
<td>600 mg every 14 d</td>
<td>7 mo†</td>
<td>9255 mg</td>
<td>$6.70 per mg</td>
<td>$62,009</td>
<td>1.5†</td>
<td>$496,072</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>NSCLC, Reck, 2009 (2)</td>
<td>7.5 mg/kg every 21 d</td>
<td>450 mg every 21 d</td>
<td>6 cycles†</td>
<td>2700 mg</td>
<td>$6.70 per mg</td>
<td>$18,090</td>
<td>0.5†</td>
<td>$434,160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>NSCLC, Pirker, 2009 (4)</td>
<td>L: 400 mg/m²; M: 250 mg/m²/wk</td>
<td>L: 600 mg; M: 375 mg</td>
<td>18 wk†</td>
<td>6975 mg</td>
<td>$5.76 per mg</td>
<td>$40,176</td>
<td>1.2</td>
<td>$401,760</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>NSCLC, Lynch, 2010 (5)</td>
<td>L: 400 mg/m²; M: 250 mg/m²/wk</td>
<td>L: 600 mg; M: 375 mg</td>
<td>13 wk†</td>
<td>5100 mg</td>
<td>$5.76 per mg</td>
<td>$29,376</td>
<td>1.3</td>
<td>$271,163</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>NSCLC, Sandler, 2006 (6)</td>
<td>15 mg/kg every 21 d</td>
<td>900 mg every 21 d</td>
<td>7 cycles†</td>
<td>6300 mg</td>
<td>$6.70 per mg</td>
<td>$42,210</td>
<td>2</td>
<td>$253,260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Glioblastoma, Friedman, 2009 (7)</td>
<td>10 mg/kg every 14 d</td>
<td>600 mg every 14 d</td>
<td>12 doses†</td>
<td>7200 mg</td>
<td>$6.70 per mg</td>
<td>$48,240</td>
<td>3.3†</td>
<td>$175,418</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>RCC, Escudier, 2009 (8)</td>
<td>400 mg twice a day</td>
<td>800 mg/d or 4 tablets per day</td>
<td>23 wk†</td>
<td>644 tablets</td>
<td>$49.67 per tablet</td>
<td>$31,987</td>
<td>2.6†</td>
<td>$147,634</td>
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<td></td>
</tr>
<tr>
<td>Ixabepilone (Ixempra)</td>
<td>Breast cancer, Hortobagyi, 2010 (9)</td>
<td>40 mg/m² every 21 d</td>
<td>60 mg every 21 d</td>
<td>5 cycles†</td>
<td>300 mg</td>
<td>$73.76 per tablet</td>
<td>$22,128</td>
<td>1.8†</td>
<td>$147,520</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>HCC, Llovet, 2008 (10)</td>
<td>400 mg twice a day</td>
<td>800 mg/d or 4 tablets per day</td>
<td>5.3 mo†</td>
<td>645 tablets</td>
<td>$49.67 per tablet</td>
<td>$32,037</td>
<td>2.8</td>
<td>$137,302</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemetrexed (Alimta)</td>
<td>NSCLC, Culeana, 2009 (11)</td>
<td>500 mg/m² twice a day</td>
<td>750 mg every 21 d</td>
<td>5 cycles†</td>
<td>3750 mg</td>
<td>$6.07 per mg</td>
<td>$22,763</td>
<td>2.8</td>
<td>$97,555</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>NSCLC, Shepherd, 2006 (12)</td>
<td>150 mg daily</td>
<td>150 mg/d or 1 tablet per day</td>
<td>2.2 mo®</td>
<td>67 tablets</td>
<td>$160.76 per tablet</td>
<td>$10,771</td>
<td>2.0</td>
<td>$64,626</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Source of average wholesale prices (AWPs) was Amerisource Bergen’s listing, which is referenced as the “BlueBook AWP” from First DataBank. BE = best estimate; HCC = hepatocellular carcinoma; L = loading; M = maintenance; NS = not statistically significant; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; RCC = renal cell carcinoma.
† Calculated for a patient of 60 kg/1.5 m².
‡ Superscript “T” refers to time of therapy as indicated in reference; superscript “P” refers to time to progression that is assumed for an oral therapy to be equal to time patient took medication.
§ For the regimen cited, the amount needed was calculated from information provided in the report. This information was either time on therapy or PFS in the case of the erlotinib trials and either daily dose or dose per cycle. Costs were calculated by multiplying the amount needed times the cost per milligram or cost per tablet.
¶ OS was for the reference cited; for NS, note that because by definition, these results were not statistically different from the control values, the amounts cited may represent therapy administered for no OS benefit at all, so that the estimate represents a best case estimate; for BE, the estimate represents a best estimate and was based on a 9.2-month survival advantage for the treated population and an estimate of 30 weeks for the expected OS as discussed in the study.
‖ QALYs is a measure of the impact of a treatment intervention. If an action gives a person an extra year of healthy life, that counts as one QALY. For these calculations, a best case outcome has assumed that any extension of OS is of good quality, although very often in oncology this is not the case.
about this statement, many examples came to mind as drugs not worth prescribing even for an incurable condition (eg, Tarceva in pancreatic cancer) (1).

The authors continue “more importantly, their policy prescription begs the question: Is limiting spending to less than $129,000 per QALY necessarily sufficient to purchase excellent care?” Obviously, less than $129,000 can purchase excellence (eg, Gleevac, which provides great benefit for “only” $92,000 per QALY). We also know that exceeding the $129,000 per QALY threshold does not always “buy the excellence” that the authors would want. Examples abound, including cetuximab and bevacizumab in non–small-cell lung cancer, bevacizumab and ixabepilone in breast cancer, bevacizumab in glioblastoma, sorafenib in kidney cancer and hepatocellular carcinoma, and erlotinib in pancreatic cancer (Table 1) (1–14). Although we agree with the authors’ assertion that “setting of thresholds is not a driver of excellent or even efficient care . . . .”, we suggested thresholds to encourage consideration and dialogue about what should count as excellence and benefit that is worth the price. We do not see a 1.2-month survival advantage as excellent at a price of $400,000—or $40,000 for that matter—nor do we think prolonging progression-free survival a few months without an overall survival benefit qualifies as excellence (2,3,5,8,9). Although views of what is excellent will vary, we think that our view may appeal to many Americans who think of a “significant” benefit in terms other than hazard ratios that ignore the magnitude of benefit and $ values that reach statistical significance only because hundreds of patients were enrolled on a study.

Furthermore, it seems appropriate to us that society and health-care payers consider quality of life and cost-effectiveness in making decisions. As noted by the authors, “In practice, the cost per QALY threshold merely delineates a cutoff between the technologies that payers claim they can afford for all and those that they will fund for no one.” But, payers need systematic and coordinated evidence, including evidence about quality of life and cost-effectiveness to make decisions about what they will pay for and what they will not.

Cohen and Looney also criticize our suggestion that studies powered to detect at most a 2-month survival advantage should be limited to interventions that will be marketed at no more than $20,000, by saying that “Determining the drug’s clinical value is not something that can or should be decided before a drug’s approval, in part because this is what markets do after approval but also because of the considerable uncertainty associated with a drug’s real-world effectiveness.” We note first that prices are often fixed even before they enter the marketplace—before a single patient has been treated—as has happened for the last three drugs approved by the Food and Drug Administration, which are Fototyn (pralatrexate; Allos Therapeutics, Westminster, CO, $30,000 per month), Istodox (romidepsin, Celgene, Summit, NJ, $76,000–$114,000 per treatment), and the prostate cancer vaccine sipuleucel-T (Provenge, Dendreon, Seattle, WA, $93,000 per patient). Furthermore, results achieved in a registration trial that enroll optimal patients with good performance status are rarely reproduced in the real world, in which the magnitude of benefit has been demonstrated repeatedly to be less and sometimes much less. Yet, price estimates (such as those in Table 1) are in fact calculated for these optimal patients, not for real-world patients who are less likely or unlikely to achieve benefit. The latter point is underscored by the results observed in the sorafenib expanded access program (14). The median overall survival of 11.5 months among patients with renal cell carcinoma was substantially less than the overall survival of 14.3–15.2 months among patients in the placebo arm in the registration trial (8,14). If the statement “the considerable uncertainty associated with a drug’s real-world effectiveness” by the authors was meant to suggest an even better outcome than in a clinical trial, we would strongly disagree because the expected outcome is of less, not of more, benefit.

We recognize that anticancer agents are frequently used off-label and that successes are sometimes found. Oncologists, however, often use off-label drugs in an experimental manner to treat terminal cancer patients without options. For too many of these terminally ill patients, benefit is not achieved and increasingly the evidence points to actual harm (15–18). Again, the need is for carefully collected evidence about drugs’ use, benefits, risks, and costs.

We are gratified that our opinions continue to generate interest. Like a good wine, the commentary may be getting better with time—because unfortunately drugs continue to be prescribed that have marginal benefits at excessive costs.

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CHRISTINE GRADY

References


Notes

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