Pem and the Cost of Multicycle Maintenance

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Klein et al.[1] present a timely analysis on the cost-effectiveness of maintenance pemetrexed (Pem) in the treatment of advanced (stage IIIB/IV) non-small cell lung cancer (NSCLC), a relatively young treatment paradigm, in this issue of the *Journal of Thoracic Oncology*. After all, recent debate over health care reform has shed a new light on rising medical costs and their consequences for national economic health. This concern is particularly germane to cancer care for which the development of expensive novel therapeutics,[2,3] limited cost controls,[4] and increases in the percentage of patients receiving all types of therapy are contributing to increased health care expenditures.[5]

In this study, the primary analysis used the results of an international phase III trial published in 2009, which demonstrated improved progression-free and overall survival in patients receiving Pem over best supportive care alone in the maintenance setting, primarily accounted for by patients with nonsquamous histologies.[6] The authors applied these results, data on adverse events, and cost estimates from a claims database as inputs to a semi-Markov model (a type of computer-based simulation of disease trajectory) to estimate life-years gained (LYGs) and the incremental cost-effectiveness ratio (ICER) of Pem maintenance therapy compared with best supportive care from the perspective of the health care payer. As secondary analyses, the authors compare Pem maintenance with the estimated ICERs for maintenance erlotinib or bevacizumab from other analyses.

The authors used the recommended methods for cost-effectiveness research,[7] including the use of intention-to-treat outcomes, applying a discount rate, providing sensitivity analyses to account for uncertainty, and using ICERs. Yet, in this study, the authors opted to measure outcomes in LYGs as opposed to the preferred quality-adjusted life-years; using the former measure will tend to make treatments of patients with advanced cancer more cost-effective than they actually are.

This study evaluated subsets based on histology (squamous versus nonsquamous), a prespecified analysis in the original study although one for which no stratification was performed. In the absence of clinical trials directly comparing Pem to either erlotinib or bevacizumab in the maintenance setting, the authors instead relied on extrapolating data from other phase III trials, limiting the quality of the model assumptions used for the secondary analyses and making these comparisons less convincing. The key result then was the finding of the primary analysis that demonstrated an ICER of $122,371 per life-year gained in nonsquamous histology NSCLC. When all NSCLC histologies were included, the ICER increased to $205,597.

So how do we use this information? To place their results into context, the authors cite the analysis by Braithwaite et al. that suggested a range for acceptable cost between $95,000 and $264,000 per LYG based on estimates of advances in health care and medical costs relative to 1950 and the benefits of insurance against the costs of noninsurance.[8] Others have proposed the cost-effectiveness of renal dialysis ($120,090 per quality-adjusted life-year) as a benchmark.[3] Regardless, these different ranges provide only theoretical guidance in the United States, where cost effectiveness analyses have no meaningful policy ramifications. The Food and Drug Administration has already approved Pem for maintenance therapy, but approval does not require or imply an assessment of

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cost-effectiveness. In addition, the Centers for Medicare and Medicaid Services remain restricted in its ability to curtail pharmaceutical costs.[4]

To some degree, these data could potentially be used by individual physicians to make treatment decisions, as suggested by a recent survey of American Society of Clinical Oncology member oncologists,[9] but it is not altogether clear how. Although 70% of survey respondents would not consider this therapy cost-effective based on their reported personal thresholds (no more than $100,000 per LYG), only 42% felt "well-prepared to interpret and use cost-effectiveness information in [their] treatment decisions." Matters are further complicated when the priorities of the general population are considered. In a 2006 cross-sectional survey conducted by the National Opinion Research Center of the University of Chicago, 73.5% of the respondents thought that the nation was spending too little on improving and protecting the nation's health.[10] In the public eye, expectations of our health care system seem to remain uncoupled to costs.

Given the estimate of cost-effectiveness in the study, it may come as a surprise for readers that the United Kingdom's National Institute for Health and Clinical Excellence (NICE) approved Pem as maintenance therapy for advanced nonsquamous NSCLC. Nevertheless, this approval was based on an estimated ICER of £47,000 (approximately US $73,000) for Pem in the same clinical setting.[11] Why was Pem nearly twice as cost-effective in the NICE analysis as it appears to be in the one from Klein et al.? The answer is simple—the cost of the drug. The model submitted to NICE assumed a drug cost of £800 (approximately US $1250) per 500 mg for patients in the United Kingdom, whereas this study assumes a drug cost twice as high for patients in the United States (Table 1). Same drug, same indication, and in fact the same underlying trial data were used to generate the estimates.

TABLE 1. Comparison of Drug Costs and ICER Estimates Based on Cost-Effectiveness Analyses Presented in NICE Approval Analysis and in Current Study

	NICE Estimates for UK[a]	Current Study's Estimates for US
Cost of pemetrexed per 500-mg vial	$1248 (£800)	$2408
ICER for nonsquamous histology	$73,323 (£47,000)	$122,371

[a] British pound to US dollar exchange rate calculated using 2010 first quarter average (1 USD = 0.641 GBP).

NICE, National Institute for Health and Clinical Excellence; ICER, incremental cost-effectiveness ratio.

That the United Kingdom is able to obtain Pem for a lower cost than it is sold for in the United States is likely a reflection of their strong regulatory approach to coverage and reimbursement. If the drug were not cost-effective, then it would not be used. So, to achieve cost-effectiveness, the manufacturer lowers the price. In the United States, the fact that Pem provides clear clinical benefit in the maintenance setting is all that is needed to ensure its use. Although we want patients to have access to such efficacious therapies, can we really expect a fundamentally cost-insensitive approach to be sustainable? Someday, perhaps, we will have a clear policy in the United States about cost-effectiveness, so that manufacturers adjust their pricing to meet prespecified thresholds. But today, our efforts to generate more and more precise estimates of cost-effectiveness analogize to the proverbial dog chasing a car down the street. He has no plan for what he will do when he catches it.

REFERENCES

1. Klein R WR, Muehlenbein C, Liepa AM, et al. Cost-Effectiveness of pemetrexed as first-line maintenance therapy for advanced nonsquamous non-small cell lung cancer. *J Thorac Oncol* 2010;5:1263–1272.
2. IMS Health Forecasts Continued Double-Digit Annual Growth of Cancer Therapeutics: Global Sales Expected to Exceed $75 Billion by 2012. 2008. Available at: http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=6e0f5e878e205210VgnVCM100000ed152ca2RCRD&vgnextchannel=41a67900b55a5110VgnVCM10000071812ca2RCRD&vgnextfmt=default#. Accessed April 21, 2010.
3. Fojo T, Grady C. How much is life worth: cetuximab, non-small cell lung cancer, and the $440 billion question. *J Natl Cancer Inst* 2009;101:1044–1048.
4. Bach PB. Limits on Medicare's ability to control rising spending on cancer drugs. *N Engl J Med* 2009;360:626–633.
5. Warren JL, Yabroff KR, Meekins A, et al. Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst* 2008;100:888–897.
6. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;374:1432–1440.
7. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996;276:1253–1258.
8. Braithwaite RS, Meltzer DO, King JT Jr, et al. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Med Care* 2008;46:349–356.
9. Neumann PJ, Palmer JA, Nadler E, et al. Cancer Therapy Costs Influence Treatment: A National Survey Of Oncologists. *Health Aff (Millwood)* 2010;29:196–202.
10. Smith T. *Trends in National Spending Priorities, 1973–2006*. Chicago, IL: University of Chicago, 2007.
11. Lung cancer (non-small-cell)—pemetrexed (maintenance): final appraisal determination. 2010. Available at: http://www.nice.org.uk/guidance/index.jsp?action=download&o=48303. Accessed April 21, 2010.