How Much Is Life Worth: Cetuximab, Non–Small Cell Lung Cancer, and the $440 Billion Question

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The spiraling cost of cancer care, in particular the cost of cancer therapeutics that achieve only marginal benefits, is under increasing scrutiny. Although health-care professionals avoid putting a value on a life, our limited resources require that society address what counts as a benefit, the extent to which cost should factor in deliberations, and who should be involved in these decisions. Professional societies, such as the American Society of Clinical Oncology, government agencies, including the Food and Drug Administration, and insurance companies should be involved. However, no segment of society is better qualified to address these issues than the oncology community. Oncologists must offer clear guidance for the conduct of research, interpretation of results, and prescription of chemotherapies. We review recent drug approvals and clinical trials and comment on their relevance to the issue of the spiraling cost of oncology therapeutics. We suggest some standards that would serve as a starting point for addressing these issues.

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The year 2008 was one with few major breakthroughs in cancer treatment. A highlight of the war on cancer at the annual meeting in 2008 of the American Society of Clinical Oncology (ASCO) was the reporting of the results of a multi-institutional European trial in which cetuximab was added to cisplatin and vinorelbine to treat patients with non–small cell lung cancer (NSCLC) (1). The overall survival (OS) advantage from adding cetuximab was 1.2 months (hazard ratio [HR] = 0.871, $P = .04$). This extra time was accompanied by a substantially higher rate of febrile neutropenia in those receiving cetuximab, along with higher frequencies of acne-like rash, diarrhea, and infusion-related reactions. Unfortunately, there were no systematic quality-of-life assessments reported to objectively determine the tolerability of the agent compared with conventional treatment.

Did the results of this trial constitute a breakthrough? According to the researchers, "Cetuximab added to a platinum-based chemotherapy sets a new standard for the first-line treatment of patients with non–small cell lung cancer" (1). And the ASCO press briefing asserted, "these findings are likely to have a significant impact on the care of patients with these types of cancer" (2). But the only reasonable conclusion is that a magic anticancer bullet aimed at an important target missed by a wide margin. Nevertheless, the presentation raised once again an even more pressing and important set of issues: What counts as a benefit in cancer treatment? How much should cost factor into deliberations? Who should decide? As oncologists, we cannot go on without answering these questions. The moral character of our specialty depends on the answers.

The Purported Benefits of Cancer Treatments

Unfortunately, the announcement of a 1.2-month prolongation of survival in NSCLC was not the first time cetuximab garnered attention for marginal benefits. The Food and Drug Administration (FDA) approved cetuximab for advanced colorectal cancer after it was shown that when combined with irinotecan, it prolonged OS by 1.7 months compared with single-agent cetuximab but not with single-agent irinotecan (3–5). Preliminary reports also indicated a marginal benefit in the front-line setting characterized by higher response rates, with an effect on progression-free survival (PFS) of at most 0.9 months (27 days) (6–9). And this prolongation of survival occurred at the expense of skin toxicity in as many as 85% of patients, including grades 3 and 4 toxicities in 18.7% (7), with skin toxicity likely to occur in 100% of those who benefited (10). Is an additional OS of 1.7 months a benefit regardless of costs and side effects?

Cetuximab is not alone among treatments offering marginal benefit at very high cost. The FDA approved the anti–vascular endothelial growth factor antibody bevacizumab (Avastin) in combination with carboplatin and paclitaxel for first-line treatment of eligible patients with locally advanced, recurrent, or metastatic nonsquamous NSCLC based on an OS increase of 2 months (11). The addition of bevacizumab to chemotherapy then became the standard of therapy for nonsquamous NSCLC, despite disagreement among lung cancer specialists regarding the actual benefit. The authors of a recent phase III trial claimed that their "study augments a growing body of evidence that combining bevacizumab with standard platinum-based chemotherapy provides important clinical benefits for patients with advanced nonsquamous NSCLC"

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(12). They concluded this after showing that compared with placebo, the addition of either low- or high-dose bevacizumab to gemcitabine and cisplatin prolonged PFS by 0.6 months in the low-dose bevacizumab group (median PFS = 6.7 vs 6.1 months for placebo; $P = .003$) and 0.4 months in the high-dose bevacizumab group (median PFS = 6.5 vs 6.1 months for placebo; $P = .03$). The duration of follow-up was not sufficient for analysis of OS. However, based on past experience, this albeit statistically significant improvement of 18 and 12 days, supported by hazard ratios for PFS of 0.75 and 0.82, may not withstand the OS test. For example, in the study in which bevacizumab was added to carboplatin and paclitaxel, the benefits in PFS (HR = 0.66) and OS (HR = 0.79) were similar, and in another trial of bevacizumab (see below), the benefit in PFS did not translate into improved OS (13). If the addition of bevacizumab does not improve OS, are 12–18 additional days of PFS a real benefit?

In breast cancer, the benefit of bevacizumab is even less, and probably nonexistent, even if measured in days. In combination with paclitaxel, bevacizumab was reported to prolong PFS by a statistically significant extent compared with paclitaxel alone (median PFS = 11.8 vs 5.9 months; HR for progression = 0.60; $P < .001$) (13). Yet, the benefit in PFS did not translate into an increase in OS. The actual benefit to the patient of this prolongation in PFS is questionable because there was no improvement in quality of life as demonstrated by the lack of statistically significant changes in scores on several validated instruments. Despite these data, the FDA approved bevacizumab for the treatment of metastatic breast cancer.

Finally, marginal benefits have not been confined to biological agents. In pancreatic cancer, the addition of erlotinib to gemcitabine improved OS a mere 10 days (median OS = 6.24 vs 5.91 months) (14). The authors noted that objective response rates were not substantially different between the groups and that patients receiving erlotinib and gemcitabine experienced higher frequencies of rash, diarrhea, infection, and stomatitis, but these were generally grade 1 or 2, albeit with dose reductions in 16% of patients and treatment discontinuation due to toxicity or refusal in 10% and 8% of patients, respectively. Again, we must ask ourselves if the additional 10 days are a benefit. Furthermore, in renal cell carcinoma, an OS advantage for sorafenib could only be demonstrated by comparing the sorafenib-treated cohort with the placebo patients who did not cross over to receive sorafenib, clearly a group of patients with a poorer prognosis, and the survival advantage was obtained at a substantial cost in terms of both toxicity and expense (15,16).

These examples challenge the oncology community to address some serious questions: What should count as a benefit in cancer? What is the minimum amount of benefit needed to adopt a therapy as the new standard? Is 1.2 months of additional life a "good" in itself? How much should the quality of that 1.2 months matter? Or the cost?

The Costs of Cancer Treatments

In the United States, 18 weeks of cetuximab treatment for NSCLC costs an average of $80 000, which translates into an expenditure of $800 000 to prolong the life of one patient by 1 year (17) (Table 1). Cetuximab is not unique in costing more than the median US household income ($50 233) (18) or a year's tuition at the finest colleges in the country (19)—bevacizumab costs $90 000 to treat an average patient (17 and Table 1). Erlotinib and sorafenib as used in the registration regimens cost approximately $16 000–$34 000 per patient (Table 1) (17). By comparison, artificial renal dialysis costs $129 090 for one quality-adjusted life year (20).

In some sense, every life is of infinite value, and we naturally avoid confronting the tension between not wanting to put a value on a life and having limited resources. But the spiraling cost of cancer care in particular makes this dilemma inescapable. We, the oncology community, cannot continue to ignore it. Such expensive therapies impose substantial burdens on patients and providers of health insurance. We must stop deluding ourselves into thinking that prescribing cetuximab, bevacizumab, erlotinib, or any of the other expensive chemotherapies and tests are an aberration, a temporary deviation from an otherwise reasonable cost trajectory. Indeed, greater than 90% of the anticancer agents approved by the FDA in the last 4 years cost more than $20 000 for a 12-week course of treatment (17). These approvals—and the use of these drugs by oncologists—signal to pharmaceutical companies our

Table 1. Estimated drug costs for indications cited in the text*

Drug (brand name)	Regimen	Dose†	Amount needed†,‡	Cost per milligram or cost per tablet	Total cost‡	Increase in OS‡
Cetuximab (Erbitux)	Loading: 400 mg/m^2; maintain: 250 mg/m^2/wk	Loading: 600 mg; maintain: 375 mg	6975 mg	$11.52/mg	$80 352	1.2 mo (1)
Bevacizumab (Avastin)	10 mg/kg every 14 d	600 mg every 14 d	13 200 mg	$6.88/mg	$90 816	1.5 mo§ (13)
Erlotinib (Tarceva)	150 mg daily	150 mg/d; 1 tablet per day	112 tablets	$140.64 per tablet	$15 752	10 d (14)
Sorafenib (Nexavar)	400 mg twice a day	800 mg/d; 4 tablets per day	692 tablets	$49.67 per tablet	$34 373	2.7 mo (15)

* Costs from *Red Book 2008 (Drug Topics Red Book)* by Harold Cohen (17). PFS = progression-free survival.

† Calculated for a 60 kg/1.5 m^2 patient.

‡ For the regimen cited, administered as in the study cited, until the time of median disease progression as reported in the published study.

§ Not statistically significant.

tolerance of such pricing, and they set a higher threshold for what society considers acceptable costs.

New Drugs as Stepping Stones

We should also not assume that approval of these expensive drugs with marginal overall benefit would necessarily lead to identification, perhaps based on molecular techniques, of a subset of patients that derives greater benefit and hence give us a greater return on our investment than was initially apparent. The recent ASCO Provisional Clinical Opinion recommending that anti–epidermal growth factor receptor (EGFR) antibody therapy should not be administered to a patient with colorectal carcinoma if a KRAS mutation in codon 12 or 13 is detected is a good start to the rational use of molecularly targeted agents (21). However, the majority of the 60%–80% of patients with colorectal carcinoma who will still receive the anti-EGFR antibody cetuximab will not derive benefit, underscoring not how far we have come but how far we must go (21). Or consider the use of erlotinib in pancreatic cancer, clearly a disease in which advances are urgently needed (14). Do we really believe that soon we will be able to identify the small percentage of patients who had some marginal benefit? Who will fund this research? And who will conduct it?

Because none of the novel therapies mentioned above has achieved cures, the majority of patients with treatment-refractory cancers eventually receive them, often in succession, adding to the financial burden to society. Although it is true that progress is often incremental—recent improvement in the treatment of colon cancer is a clear example—advances are likely to be discarded or trumped by completely new therapies (eg, Gleevec's displacement of interferon and stem cell transplant in chronic myelogenous leukemia). Thus, not all advances are building blocks for the future, and this expectation should not justify expenditures for marginal benefits in patients with advanced disease. An example of this is the recent observation in colorectal cancer that addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab resulted in shorter PFS and inferior quality of life—an observation reinforced by similar results with panitumumab (22,23). Furthermore, although some agents (eg, Trastuzumab) (24,25) approved in the metastatic setting may also have benefit in the first-line setting, a better outcome in first-line therapy is not guaranteed, especially for drugs with marginal benefits. For example, a recent study examining the potential benefits of treatment with sorafenib (Nexavar) in patients with untreated advanced renal cancer found a minimal difference in median PFS when the drug was administered as first-line therapy (median PFS = 5.7 months) compared with its previous benefit in second-line therapy (median PFS = 5.5 months) (15,26). Unfortunately, differences in OS were not reported—an important omission—because if in an earlier setting a drug has a benefit in PFS that is marginal and similar to that in patients with advanced disease, it may not result in a statistically significant OS advantage. For the patient with advanced disease and at best 12 months of expected survival, an extra month or two might be statistically meaningful, but it may not be so for a patient at an earlier point in their disease expected to survive a few years.

What Is to Be Done?

Who should tackle this problem? ASCO and other professional societies have an essential role in defining standards of care. If a treatment with marginal benefit is declared a new standard and a clinically or statistically significant gain at a plenary presentation of its annual meeting and this is featured at press briefings, ASCO effectively endorses—or appears to endorse—that view. Sadly, some years do not produce breakthroughs in treatment of sufficient importance to fill a plenary session. This does not mean that marginal benefits should be showcased; other types of presentations merit consideration for plenary session presentations. We must not let *P* values or the increasingly popular hazard ratio define success. For drugs that target EGFR, which has been long touted as an important target in lung and colorectal cancers, marginal benefit in NSCLC and colorectal cancer is nothing less than a major disappointment. Attempts to view this otherwise place hope above data, experience, and reality. We must recognize that professions can regulate themselves and, in fact, that is part of the role of a professional society. ASCO should lead the way in engaging oncologists and the public in dialogue about what should count as a benefit. Oncologists should feel supported if they decide that for a given patient or group of patients, the marginal benefit is not worth the cost. Cancer researchers should be clear about the benefit they are trying to achieve in a trial, how it will be measured, and what it will mean for the field.

The FDA must also shoulder responsibility. It should reconsider the validity of PFS as an endpoint, especially when OS is not affected and the advance in PFS is not accompanied by an improvement in quality of life. More importantly, trial design is critical for determining what magnitude of survival advantage will pass that magical *P* value of .05. In the cetuximab trial, the 1.2-month survival advantage achieved statistical significance because the inclusion of 1125 patients ensured that a small difference would reach statistical validity. The FDA should encourage trials powered for larger differences and discourage those looking for marginal differences. Trials that demonstrate no survival advantage or prolonged survival of only 1 or 2 months should be subject to greater scrutiny.

Insurance companies and government health agencies should also assume some responsibility. Although patients with end-stage renal disease might receive greater financial support overall than cancer patients because they live longer, we should not advocate spending more for cancer patients than for those with end-stage renal disease. Other developed countries spend less than $129 090 for an extra year of life and this should be sufficient to buy excellent care (27,28). In Great Britain, for example, the National Institute for Clinical Excellence has established a maximum threshold of €30 000 per quality-adjusted life year. Insurance companies and government agencies should benchmark therapies to an agreed on amount. If this were done, Americans would still receive excellent care. This would not inhibit innovation but direct it toward interventions that produce clinically significant improvements in health outcomes or ones that can be priced at a lower level commensurate with their marginal benefits. Government agencies could engage the public—not just interested drug companies, oncologists, and patient advocates—in

deliberations regarding how much they are willing to pay to achieve certain levels of benefit. Knowing the maximum Americans are willing to spend could transform pharmaceutical companies and their practices because they recognize that to extend indications, they must compromise on price. Thus, a small survival advantage would only be acceptable if a company were willing to substantially reduce a drug's price in exchange for a larger market share. For those unwilling or unable to reduce prices, only smaller studies that detect larger differences should be tolerated. Such changes would streamline drug development, reduce costs, and lead to more rapid completion of clinical trials. Rather than hamper research and development, this would lead to a greater focus on a better pipeline with less redundancy across companies. After all, do we need 10 companies developing similar drugs for each potential target?

Many Americans would likely not regard a 1.2-month survival advantage as "significant" progress, the much revered *P* value notwithstanding. But would an individual patient agree? Although we lack the answer to this question, we would suggest that the death of a mother of four at age 37 years would be no less painful were it to occur at age 37 years and 1 month, nor would the passing of a 67-year-old who planned to travel after retiring be any less difficult for the spouse were it to have occurred 1 month later. Indeed, although one hopes that insurance companies never offer patients the choice between receiving a therapy with marginal benefit and receiving a fraction of the cost as a monetary disbursement, it would not be surprising to see patients opt for the disbursement to leave to their loved ones or to spend with them while they are alive.

The Responsibility of Oncologists

Ultimately, however, what counts as a benefit in cancer treatment and how much cost should factor into deliberations are not ethical problems that can be relegated to others. No segment of society is better qualified to address these issues than the oncology community. It is time to confront these issues, lest others confront them for us. Oncologists must offer clear guidance both in the conduct of research and in prescribing chemotherapies. To begin the discussion in the profession, we suggest the following standards:

1. Research studies that are powered to detect a survival advantage of 2 months or less should only test interventions that can be marketed at a cost of less than $20 000 for a course of treatment, which is a monetary value consistent with the cost of one quality-adjusted life year in patients treated with artificial renal dialysis ($129 090). Similarly, a study designed to detect a 4-month advantage can test a therapy that will cost up to $30 000 per patient. The corollary of this is that we should demand that drugs already approved be priced accordingly. For example, it has been estimated that to be cost-effective even at the $100 000 per quality-adjusted life year level, the retail price of 6 months of erlotinib would have to be reduced by 80% (29).
2. Drugs shown to be active in one subset of patients should be advocated, approved, and prescribed for that subset only. The marginal benefit, if any, which may be achieved in other patients should not be an excuse to administer a therapy even if it is decided that there is nothing further to be done.
3. FDA-approved indications should be strictly adhered to. If the FDA approves a drug for first-line therapy, it should not be used in a second-line setting unless evidence is obtained that sequential therapies provide meaningful benefit that outweighs toxicities. Without such evidence, insurance companies should deny coverage, and physicians should not administer the drug.
4. The all too common practice of administering a new, marginally beneficial drug to a patient with advanced cancer should be strongly discouraged. In cases where there are no further treatment options, emphasis should be first on quality of life and then cost. Although we recognize that oncologists are faced every day with dying patients who still want to pursue further therapy, we must avoid the temptation to tell a patient that a new drug (eg, single-agent bevacizumab or cetuximab) is available if there is little evidence that it will work better than established drugs (eg, oral etoposide or cytoxan) that could be offered at a miniscule fraction of the cost and with possibly less toxicity.
5. For therapies with marginal benefits, toxic effects should receive greater scrutiny. Consideration could be given to developing a cumulative toxicity index that considers toxic effects—their grade, duration, and actual impact on quality of life—and allows for a more uniform comparison.

We must deal with the escalating price of cancer therapy now. If we allow a survival advantage of 1.2 months to be worth $80 000, and by extrapolation survival of 1 year to be valued at $800 000, we would need $440 billion annually—an amount nearly 100 times the budget of the National Cancer Institute—to extend by 1 year the life of the 550 000 Americans who die of cancer annually. And no one would be cured.

The current situation cannot continue. We cannot ignore the cumulative costs of the tests and treatments we recommend and prescribe. As the agents of change, professional societies, including their academic and practicing oncologist members, must lead the way. The time to start is now.

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Notes

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