Proposal for a Novel Methodology to Screen And Score Cost Versus Survival for Anticancer Drugs in Metastatic Disease: Could Cost Weigh in Evaluation?

By Helmy M. Guirgis, MD, PhD

University of California, Irvine, CA

Abstract

Purpose: Rising costs of anticancer drugs prompt concerns about their approval, use, and affordability. A methodology was developed to evaluate cost versus survival for anticancer drugs in metastatic breast cancer and non-small-cell lung cancer (NSCLC).

Methods: Costs of evaluated drugs were calculated by using average wholesale prices in US dollars. Ratios of cost to day of survival (cost/survival/d) were obtained by dividing costs of the entire treatment by reported median survival gain in days. A crude score of 100% was assigned to a cost/survival/d of less than \$25, and 0% to a cost/survival/d of more than \$750. A strategy was designed to correct for overall survival (OS) versus progression-free survival (PFS), adverse effects, and quality of life.

Results: In breast cancer, PFS scores of bevacizumab varied between 0% and 60%. In NSCLC, OS scores of bevacizumab improved from 0% to 50%, as a result of histology, lower prices, and extended therapy. Gefitinib and erlotinib PFS scores were 80% and 70%, respectively. Correction for longer survival with erlotinib resulted in similar scores. In maintenance therapy, the OS score for pemetrexed was 70% as compared with 25% for erlotinib. Generic drugs scored 70% to 90%.

Conclusion: Cost/survival varied with the number of cycles. In breast cancer, bevacizumab scores failed to justify its use. In NSCLC, 10 cycles of bevacizumab scored 0%. Scores improved with extended treatment and lower prices. Scores for gefitinib and erlotinib would support their approval. Erlotinib was preferred because of longer PFS. Results tended to endorse maintenance pemetrexed but not erlotinib. Generic drugs demonstrated high scores. Cost/survival could weigh in drug evaluation.

Introduction

Rising costs of anticancer drugs have raised questions about their affordability, use, and cost effectiveness.¹⁻⁴ Multiple end points in cancer outcome^{5,6} and evolving adverse effect (AEs) in an era of targeted therapy⁷ complicate a fair assessment of cost effectiveness.⁸ In Canada, Europe, and Australia, approval of anticancer drugs with limited cost effectiveness has been curtailed. Drug approval authorities have issued controversial rulings. The National Institute for Health and Clinical Excellence (NICE) for England and Wales rejected bevacizumab as a first-line treatment for advanced and/or metastatic human epidermal growth factor receptor 2 (HER2) –negative breast cancer. However, the European Medicines Agency (EMA) approved marketing of bevacizumab in combination with paclitaxel. Approval and subsequent denial of bevacizumab for treatment of breast cancer by the US Federal Drug Administration (FDA) were not based on the drug's cost. The decisions were based on lack of overall survival (OS), wide variation in progression-free survival (PFS), and potentially fatal AEs.⁹⁻¹¹ Erlotinib, a drug used in second- and third-line treatment of non-small-cell lung cancer (NSCLC),¹² was approved in Canada and the United States. However, Bradbury et al¹³ reported that erlotinib was marginally cost effective at CDN \$95,000 for each year of life gained.

In the current global economic climate, a fresh approach to the process of cost effectiveness analysis is needed. To that end, this study reviewed cost effectiveness and rationales for approval

or rejection of anticancer drugs by the US Oncological Advisory Committee (ODAC), FDA, and NICE. The drugs evaluated included erlotinib, gefitinib, bevacizumab, trastuzumab, cetuximab and pemetrexed, and sipuleucil-T.¹⁴ The main study objectives were (1) develop a cost methodology that placed limits on cost versus survival for anticancer drugs; (2) apply the methodology to drugs commonly used in first-line treatment of metastatic breast cancer and NSCLC; (3) consider the possibility that cost could be a factor in drug evaluation.

Methods

The approved drug dosage, frequency of administration, and number of cycles were adhered to as much as possible. Average wholesale prices (AWP) in US dollar were used. The cost of each drug was determined for a 70 kg, 80 kg, or 1.7/m² sized patient for the entire treatment course. Costs of generic drugs were estimated at flat rates of \$4,800 to \$7,200. Costs of ancillary treatment often required with cytotoxic agents were added to cost of the evaluated drug and included in cost per survival per day (cost/survival/d). Costs associated with drug preparation, wasted or outdated vials, and treatment of drug-related complications were not included. Ratios of cost/survival/d were obtained by dividing the total costs of the evaluated drug by median survival gain in days as reported at the first disclosure of phase III trials. A 100% score was assigned to a cost/survival/d of less than \$25. Percentage scores were assigned in decreasing

and proportionate order, with 0% assigned to a cost/survival/d of more than \$750 (Table 1). Results were expressed as cost/survival/d and crude scores of cost/PFS or cost/OS. Scores were then corrected by using three modifiers: (1) survival: 15% was subtracted for lack of significant OS. Drugs that demonstrated PFS of 6 months were exempt. (2) quality of life (QoL): 5% to 10% was added for stabilization and improvement in QoL, as contrasted with 0% for deterioration. (3) AEs: Common Terminology Criteria for Adverse Effects version 3.0 was used. Assessment was based on AEs of the whole combinations rather than of individual drugs. AEs 5% to 10% higher than those of controls and potentially fatal¹⁵⁻¹⁷ were penalized by subtracting 15%. For lesser grades of AEs,^{12,18,19} 0% to 10% was deducted depending on drug profiles and combinations.

Results

The maximum AWP of > 90% of the evaluated anti-cancer drugs for the entire treatment course were < \$1,500/survival/d. Because AWP are usually much lower than the actual acquisition costs, a scale was constructed with 0% scores and references of \$750 cost/survival/d. The methodology was initially tested by using various approved and rejected drugs. Two examples are presented to demonstrate its applicability. In first-line metastatic colorectal cancer, bevacizumab 5.0 mg/kg, in combination with irinotecan and fluorouracil, administered every 2 weeks prolonged OS by 141 days.²⁰ At an AWP of \$6.6 per mg in an 80-kg patient, the total cost of 20 cycles was estimated at \$52,800, with a cost/survival/d of \$374, corresponding to an OS crude score of 40%. The score was corrected by subtracting 15% for potentially fatal AEs.¹⁷ Stabilization in QoL by bevacizumab was rewarded by adding 5%. After adjustments, the corrected score decreased to 30%. Bevacizumab is approved for colorectal cancer in the United States, but its use is still being questioned by NICE and EMA. The second example was trastuzumab which, in combination with paclitaxel, prolonged OS by 144 days in first-line treatment of metastatic HER2-positive breast cancer.²¹⁻²³ Table 2 shows a cost/survival/d of \$402 and a crude score of 35%. Trastuzumab in combination with anastrozole²⁴ scored 60% in hormone- and HER2-positive cancers. The drug is universally approved in first-line treatment of HER2-positive breast cancer.

Breast Cancer

Bevacizumab plus paclitaxel⁹ was reported to prolong PFS by 177 days in first-line treatment of advanced and metastatic breast cancer.⁹ Using 26 bevacizumab cycles at an AWP of \$6.60 per milligram in a 70-kg body weight, the total cost was estimated at \$120,129, with a crude score of 10% (Table 2). Lowering the cost of bevacizumab by 33% increased the score to 25%. Using seven cycles as a basis for comparison, the costs/survival/d of bevacizumab in combination with paclitaxel, capecitabine, and docetaxel⁹⁻¹¹ were \$183, \$558, and \$851, corresponding to scores of 60%, 20%, and 0%, respectively.

Table 1. Assignment of Scores to Cost/Survival/Day

Survival Gain (days)	Hazard Ratios	Cost/Survival/Day (\$)	Crude Scores (%)
≥ 360	< 0.10	< 25	100
330-359	0.10-0.19	25-49	90
300-329	0.20-0.29	50-99	80
270-299	0.30-0.39	100-149	70
240-269	0.40-0.44	150-199	60
210-239	0.45-0.49	200-249	55
180-209	0.50-0.54	250-299	50
150-179	0.55-0.59	300-349	45
120-149	0.60-0.64	350-399	40
90-119	0.65-0.69	400-449	35
60-89	0.70-0.74	450-499	30
45-59	0.75-0.79	500-549	25
30-44	0.80-0.84	550-599	20
21-29	0.85-0.89	600-649	15
14-20	0.90-0.94	650-699	10
7-13	0.95-1.0	700-750	5.0
< 7	> 1.0	> 750	0

NOTE. A scale was constructed with 100% scores being assigned to cost per day of survival (cost/survival/day) of < \$25 and 0% to > \$750. Survival gain and hazard ratios were used as a reference and guide. Results were expressed as % crude scores of cost/PFS or cost/OS. At the 50% score, cost/survival ranged between \$250 and \$299. The average total cost of evaluated drugs was \$43,165 with a median of \$28,938.

Abbreviations: OS, overall survival; PFS, progression-free survival.

NSCLC

Generic drugs and monoclonal antibodies (MOAs). In the present study, costs of generic drugs were set at \$4,800 to \$7,200, higher than purchase prices, in view of shortages and rising costs. In first-line therapy of metastatic NSCLC, cisplatin, paclitaxel, and vinorelbine^{25,26} demonstrated low cost/OS and 70% to 90% crude scores. Costs of hydration, antiemetics, and bone marrow growth factors added up to \$8,820, increasing the cost/survival/d to \$99 and decreasing the scores to 80%. Addition of cetuximab to chemotherapy prolonged OS by a significant 36 days in the FLEX study (Study of Cisplatin/Vinorelbine/Cetuximab as First-Line Treatment of Advanced Non Small Cell Lung Cancer),²⁷ at a cost/survival/d of \$720 and score of 5%. High epidermal growth factor receptor (EGFR) expression resulted in an OS gain of 72 days,²⁸ raising the crude score to 40%. Using bevacizumab, the AVAIL study (Phase III Study of Avastin Plus Chemotherapy in First-Line Advanced, Non-Squamous, Non-Small Cell Lung Cancer)¹⁶ demonstrated a significant 18-day OS gain in nonsquamous carcinoma at a cost/survival/d of \$1,348 and a crude score of 0% score. In the United States, bevacizumab in combination with paclitaxel and carboplatin was approved after reports of the E4599 study of a significant OS gain of 60 days in nonsquamous cell disease.¹⁵ Using seven to 10 cycles, cost/survival was \$809 and \$1,155, respectively with 0% scores. Histology-based selection of adenocarcinoma increased the OS gain to 120 days,²⁹ raising the score to 20%. Continuation of bevacizumab

Table 2. Crude and Corrected Scores in Breast Cancer

Drug Regimen	Cost of Entire Course (\$)	Survival Gain (days)		Cost/Survival/Day (\$)	Crude Scores (%)		Corrected Scores, Suggested Modifications for OS, QoL, and AEs (%)
		OS	PFS		Cost/OS	Cost/PFS	
Paclitaxel ± bevacizumab, 10 mg/kg every 2 weeks							
7 cycles	32,340		177	183		60	35*
10 cycles	46,200		177	261		50	25
20 cycles	92,400		177	522		25	0
26 cycles (E2100) ⁹	120,120		177	679		10	0
26 cycles (suggested price)	90,090		177	509		25	0
Docetaxel ± bevacizumab 15 mg/kg, every 3 weeks for seven cycles ¹⁰	48,510		57	851		0	0
Chemotherapy, capecitabine ± bevacizumab 15 mg/kg every 3 weeks for seven cycles (RIBBON-1) ¹¹	48,510		87	558		20	0
Paclitaxel ± trastuzumab for 52 weekly cycles, HER2 positive ²¹⁻²³	57,876	144		402	35		30†
Anastrozole ± trastuzumab weekly for 1 year, HER2 positive, EGFR negative (TAnDEM) ²⁴	57,876	339		171	60		55

NOTE. Survival, quality of life (QoL), and adverse events (AEs) could vary with the number of cycles. It is unclear whether 7-10 cycles of bevacizumab could result in a progression-free survival (PFS) gain of 177 days. Value correction of QoL and AEs might differ from one investigator to another. Correction of crude scores except for examples was left to the discretion of treating physicians.

Abbreviations: E2100, Eastern Cooperative Oncology Group Trial 2100; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; RIBBON, A Study Evaluating the Efficacy and Safety of Bevacizumab in Combination With Chemotherapy in Untreated Metastatic Breast Cancer; TAnDEM, Trastuzumab Plus Anastrozole Versus Anastrozole Alone for the Treatment of Postmenopausal Women With Human Epidermal Growth Factor Receptor 2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer.

* 15% subtracted for lack of OS, 15% subtracted for AEs, 5% added for gain in QoL.

† 10% subtracted for AEs, 5% added for QoL.

therapy resulted in an OS gain of 321 days.³⁰ Using 20 cycles at an AWP of \$138,600, the cost/survival/d was \$431 at a crude score of 35%. Reducing the cost by 33% to \$92,400 further increased the score to 50%.

Tyrosine kinase inhibitors (TKIs). Gefitinib and erlotinib prolonged PFS by 147 and 255 days, respectively,³¹⁻³³ in first-line treatment of patients with NSCLC who harbored *EGFR* mutations. Our results demonstrated a cost/survival/d of \$83 and \$113 with gefitinib and erlotinib, respectively, corresponding to crude scores of 80% and 70%. The drugs were penalized by subtraction of 5% for AEs and rewarded 10% for improvement in QoL. The long PFS gain with erlotinib resulted in a corrected score of 75% compared with a corrected score of 70% for gefitinib, despite its lower AWP (Table 3).

Maintenance therapy. Pemetrexed increased OS by 156 days³⁴ at a score of 70%. In comparison, erlotinib demonstrated a 36-day OS gain,³⁵ with a score of 25%. In patients whose disease had stabilized during initial therapy and who received maintenance treatment with erlotinib, Coudert et al³⁶ recently reported an improvement in OS gain of 69 days, which raised the score to 50%.

Discussion

The economic recession has forced some patients with cancer to discontinue life-extending medications.³⁷⁻³⁹ Thus it was thought timely, if not necessary, to design tools that would place limits on the cost of anticancer drugs. The present study

proposed a two-step methodology for evaluation of cost versus survival. The first step was designed as a screening tool, with results expressed as percentage crude scores. The second step involved the use of modifiers to adjust for lack of OS and potentially fatal AEs by deduction of 15%. Stabilization or improvement in QoL was compensated by the addition of 5% to 10%. Results were expressed as percentage corrected scores.

The proposed methodology was based on the design of a scale that allocated a crude score of 100% to drugs demonstrating survival of more than 360 days and a cost/survival/d of less than \$25 and a score of 0% to a cost/survival of more than \$750. It is rather difficult to compare the \$750 cost/survival/d limit with previous estimates, which ranged from \$67,215 per year of life gained to \$380,000 per year of adjusted QoL.^{1,2,8} In our methodology, 40% to 60% scores were assigned to a cost/survival/d between \$150 and \$399. Our thresholds seem to be closer to the affordable range of \$65,000 to \$100,000 that North American and Western societies and patients are willing to pay.^{1,2,13} Adjustments in cost/survival/d upward to \$1,500 or downward to \$250-\$500 could easily be done by using simple correction factors to suit the economies of different countries. Costs of drugs paired with the evaluated drugs bevacizumab, cetuximab and trastuzumab, pemetrexed, erlotinib, and gefitinib were not included in the calculations. In addition, costs of drug preparation, drug administration, and treatment of AEs (notwithstanding hospitalizations) were excluded. Such expenditures might cost several times more than the drug evaluated. Had some of the hidden and

Table 3. Crude and Suggested Corrected Scores in NSCLC

Drug Regimen	Cost of Entire Drug Course (\$)	Survival Gain (days)		Cost/Survival/Day (\$)	Crude Scores (%)		Corrected Scores, % Suggested Modifications OS, QoL and AEs (%)
		OS	PFS		Cost/OS	Cost/PFS	
Cisplatin + vinorelbine versus control	4,800	138		38	90		90*
Platinum doublets versus single agent, elderly ²⁵	7,200	72		100	70		70
Cisplatin + vinorelbine versus cisplatin ²⁶	4,800	60		80	80		80
Cisplatin + vinorelbine ± cetuximab for 10 cycles (FLEX) ²⁷	25,906	36		720	5		0†
High EGFR versus low ²⁸		72		360	40		30
Paclitaxel + carboplatin ± bevacizumab 15 mg/kg every 3 weeks							
Nonsquamous, 7 cycles	48,510	60		809	0		0‡
Nonsquamous, 10 cycles (E4599) ¹⁵	69,300	60		1,155	0		0
Adenocarcinoma, 10 cycles ²⁹	69,300	120		577	20		10
Nonsquamous, 20 cycles ³⁰	138,600	321		431	35		25
Nonsquamous, 20 cycles (suggested price) ³⁰	92,400	321		287	50		40
Cisplatin + gemcitabine ± bevacizumab 7.5 mg/kg every 3 weeks for 7 cycles (AVAL) ¹⁵	24,255	18		1348	0		0
Gefitinib 250 daily versus carboplatin + paclitaxel							
For 6 months	12,252		147	83		80	70§
For 12 months, mutated <i>EGFR</i> ^{31,32}	24,504		167			60	50
Erlotinib 150 mg daily versus carboplatin/gemcitabine							255 days PFS; lack of OS (0)
For 6 months, mutated <i>EGFR</i> ³³	28,938		255	113		70	75
For 12 months	57,876		227			55	60
Maintenance erlotinib 150 mg daily							
For 4 months without progression, all patients irrespective of EGFR status or histology ³⁵	19,292	36		536	25		Stable QoL (+5.0)
Maintenance erlotinib for stable disease, including all squamous and nonsquamous, EGFR positive and negative, for 4 months (SATURN) ³⁶	19,292	69		279	50		50
Maintenance pemetrexed every 3 weeks versus supportive care, for 4 cycles without progression; nonsquamous ³⁴	21,320	OS	156	137	70		70

NOTE. Costs of ancillary drugs could be included in the cost per day of survival (Cost/Survival/Day). Treatment of AEs of cisplatin and cytotoxic drugs by hydration, antiemetics, and bone marrow growth factors would add an estimated cost of \$8,820, raising the cost/survival/d to \$99 and lowering the scores to 80%. Abbreviations: AEs, adverse effects; AVAL, Phase III Study of Avastin Plus Chemotherapy in First-Line Advanced, Non-Squamous, Non-Small Cell Lung Cancer; EGFR, epidermal growth factor receptor; FLEX, Study of Cisplatin/Vinorelbine/Cetuximab as First-line Treatment of Advanced Non Small Cell Lung Cancer; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SATURN, A Double-Blind, Randomized, Phase III Study of Maintenance Erlotinib Versus Placebo Following Nonprogression With First-Line Platinum-Based Chemotherapy in Patients With Advanced NSCLC.

* 5% subtracted for AEs, 5% added for QoL.

† 10% subtracted for AEs.

‡ 15% subtracted for AEs, 5% added for QoL.

§ 15% subtracted for lack of OS, 5% subtracted for AEs, 10% added for QoL.

overt costs been accounted for, the toll would be much higher than what most societies and patients could bear.

There are a number of advantages in our methodology. The scoring system could be applied to cost evaluation of modalities other than drugs (eg, radiation or surgery). The methodology could also be used to evaluate drugs used in the treatment of nonmalignant disease. The current methods of determining cost effectiveness are tedious and time consuming. In contrast, using our cost-versus-survival approach is straightforward and can be performed in a few minutes or less. Changes in prices, survival, duration of treatment, and/or number of cycles were easy to account for. An unexpected finding was that cost/survival was dependent on the number of cycles of costly drugs.

Changes in the number of cycles are usually needed for patients whose disease is either responsive or resistant to treatment. Versatility renders our methodology amenable to such changes, as well as to computerization and widespread application by drug authorities, drug companies, physicians, and nurses. An added advantage was the uniform expression of survival in days rather than in differing units of days, weeks, or months, which could be confusing. It is easier to communicate to patients the dollar amount spent to provide 1 day of added survival than 1 year of life gained.

Breast Cancer

In the E2100 study (Eastern Cooperative Oncology Group), approximately 80% of patients continued bevacizumab therapy

until disease progression. It is unclear whether a gain of 177 days⁹ could be obtained by using seven to 10 cycles. The variation in bevacizumab scores from 10% to 60% was primarily related to the wide range in the magnitude of PFS gain. The low crude and corrected scores were partly related to potentially fatal AEs and lack of OS. Lowering the cost of bevacizumab by 33% resulted in an increase in the scores from 10% to 25%. A \$90,090 yearly cost is still too high to pay for inconsistent PFS gain. Our results would support the November 2011 decisions by the FDA to revoke approval for the use of bevacizumab in breast cancer. It is worth noting that the EMA recommended market approval of bevacizumab/paclitaxel in this setting.

NSCLC

Generic drugs and MOAs. It was interesting to compare the cost/survival of generic drugs with those of MOAs. In the present study, the lowest cost/survival/d and highest scores were attained mostly by inexpensive generic and chemotherapeutic drugs, in contrast to the highest cost/survival and lowest scores demonstrated by MOAs. However, the scores of cytotoxic drugs were disproportionately decreased after correction for cost of ancillary treatment, AEs, and QoL. Of interest, out of 30 drugs and cycles analyzed in the present study, costs/survival/d of four bevacizumab combinations exceeded the \$750 limit. Physicians need to become more conscious of costs, discuss costs with patients,² and be persuaded whenever possible to consider and prescribe generics.

Using cetuximab in the FLEX study of first-line treatment of metastatic NSCLC, the cost/survival/d was \$720, corresponding to a score of 5%. The high cost of cetuximab has probably been a limiting factor in its use in this setting. The recent reports of an increase in OS from 36 to 72 days with high EGFR expression²⁸ warrant further confirmation. The addition of bevacizumab chemotherapy has been investigated in two major studies in metastatic NSCLC. Cisplatin and gemcitabine in the AVAIL study¹⁶ resulted in an 18-day gain in OS. In the E4599 study,¹⁵ bevacizumab/paclitaxel/carboplatin prolonged OS by 60 to 120 days.²⁹ Using seven to 10 bevacizumab cycles, our analysis showed high cost/survival/d and 0% scores, raising concerns about the cost effectiveness and affordability of bevacizumab. However, continued bevacizumab therapy until progression using paclitaxel/carboplatin was reported to improve OS by 321 days.³⁰ Using 20 cycles of bevacizumab at an AWP of \$138,600, the score improved to 40%, with a further increase to 50% by lowering the cost to \$92,400. The number of cycles required until, and after, progression is unclear. Confirmation of the extent of OS gain by extended therapy is warranted to justify such a high cost. There are conflicting data to support continuation of therapy until progression in NSCLC.^{30,40} Mechanism and continuation of therapy to or beyond progression have been documented in breast and colon cancers.^{41–43} Should genomic markers such as HER2 in breast,²¹ KRAS in colon,⁴⁴ and EGFR in NSCLC^{45,46} be found to identify a subset of patients who would respond or be spared toxicity, bevacizumab could become more cost effective.

TKIs. The use of gefitinib and erlotinib in first-line treatment of metastatic NSCLC has been widely accepted. Lopez et al⁴⁷ recently reported that gefitinib was cost effective in the treatment of patients who harbor *EGFR* mutations. In the present study, the prolonged PFS gain, limited AEs, and improvement in QoL^{31,33,46} resulted in high crude and corrected scores for erlotinib and gefitinib. Our cost analysis would endorse the use of one or both drugs as first-line treatment and is in agreement with recent National Comprehensive Cancer Network guidelines.⁴⁸ The small difference in scores between gefitinib and erlotinib was reversed by the longer PFS with erlotinib, making the case for erlotinib as the preferred drug.

Maintenance therapy. After first-line therapy for nonprogressive NSCLC,³⁴ pemetrexed demonstrated a score of 70%, almost three times that of erlotinib. An increase in OS gain from 36 to 69 days with erlotinib was recently observed in patients with stable disease,^{35,36} with further increase by selection of EGFR-positive mutants. In the United States, erlotinib was approved for maintenance treatment of both squamous and adenocarcinoma, in contrast to pemetrexed, which was approved for adenocarcinoma. There is a growing tendency to use pemetrexed as first-line treatment, raising questions about its use in maintenance of previously pemetrexed-treated patients. At present, our results would still endorse maintenance pemetrexed but would tend not to support approval and/or use of erlotinib. Of interest, the FDA approved maintenance erlotinib, against the recommendations of ODAC.

Limitations

The main limitation lies in the quantization of AEs and QoL. The assignment of values to these variables, though relative, was arbitrary and could vary from one investigator to another. Corrections were therefore deliberately left to the discretion of the treating physicians. The maximal cost of the entire treatment course or per year of survival by an evaluated drug was \$120,120. Adjustments in the \$750 cost/survival/d upward to \$1,500 or downward to \$250–\$500 could easily be done without changes in the scores by using simple correction factors. Acquisition prices are usually less expensive than the AWP's quoted in this study, depending on the amount purchased.⁴⁹ Cost/survival could be easily calculated by dividing acquisition costs by the median survival gain. Scores for erlotinib used in second- or third-line treatment of NSCLC¹² and eribulin⁵⁰ and ixabepilone^{51,52} in refractory breast cancers ought not to be compared with scores from first-line treatment. Survival can be a moving target at any time point on the survival-time curve. Gain, loss, or change of one type of survival to another might occur as results mature. Costs change as generic versions of drugs become available.

In the present study, use of response rates was avoided.⁵ OS and survival surrogates such as PFS were used. Determination of appropriate end points in cancer outcomes is a complicated issue and was outside the scope of this investigation. Lack of clarity regarding evaluation of survival outcome could partly explain the controversy surrounding drug approval. The rela-

tive weights of OS versus PFS, to the best of my knowledge, have not been previously addressed. In the present study, scores for PFS were lowered arbitrarily by 15% from the corresponding OS scores. Whether 15% represents a reasonable value deduction is open to debate. Correction for QoL and AEs introduced additional sources of subjectivity and error. Adjustments were left therefore, except for examples, to the discretion of treating physicians.

Within the scope of the law, drug authorities set policies and trends, as well as hold the key to drug approval.^{40,53} In contrast to US practices, costs are tied by law to the budgetary process by NICE in the United Kingdom and the Pharmaceutical Benefits Advisory Committee of Australia. The Centers for Medicare & Medicaid Services officials in the United States were appointed to keep a vigilant eye on costs, with the ultimate goal of cost containment. Economic evaluations of targeted therapy might provide support for decision makers.⁵⁴ The US laws might need to be amended so that cost/survival could weigh in evaluation of drugs with borderline survival outcome.

Conclusions

A rapid and versatile methodology was proposed to screen and score cost/survival of anticancer drugs in first-line treatment of metastatic cancers. Limits of \$750 per day of survival were placed on the cost of evaluated drugs. Modifiers were suggested to correct for type of survival, AEs, and QoL. In contrast to MOAs, generic cytotoxic drugs demonstrated the lowest cost/survival and highest scores. Cost/survival increased after accounting for ancillary treatment and was dependent on the

number of cycles. In first-line treatment of metastatic breast cancer, cost/PFS of bevacizumab failed to justify its approval and use. In NSCLC, OS scores of seven to 10 cycles were 0% but improved with histology, lowering AWP, and continuation of therapy until progression. The relatively high scores of gefitinib and erlotinib would endorse the approval of one or both drugs in NSCLC. However, erlotinib was preferred because of its longer PFS. In maintenance therapy of nonprogressive disease, cost/survival analysis supported the use of pemetrexed but tended not to support approval of erlotinib. Whether the methodology could accelerate the drug approval processes and circumvent controversial decisions by weighing for or against drugs with inconclusive survival outcome remains to be seen.

Accepted for publication on December 13, 2011.

Acknowledgment

I acknowledge the memories of patients and veterans who I had the privilege to serve. Special thanks to Randolph Holcombe, MD (University of CA, Irvine); Frank Dunphy, MD (Duke University Medical Center, Durham, NC); and Bradley J. Monk, MD (Creighton University, St. Joseph's Hospital and Medical Center, Phoenix, AZ).

Author's Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

Corresponding author: Helmy M. Guirgis, MD, 24806 Sea Crest Drive, Dana Point, CA, 92629; e-mail: Cancerguir@gmail.com.

DOI: 10.1200/JOP.2011.000390.

References

- Negrier S, Remak E, Brown R, et al: Economic evaluation of sunitinib vs. interferon- α (Ifn- α) in first line metastatic renal cell carcinoma (mRCC). Presented at the 14th European Cancer Conference, 2007 (poster 4514)
- Dale W, Fojo T: Should oncologists discuss the cost of treatment with patients? *Hemonctoday: Clinical News in Hematology and Oncology*. www.hemonctoday.com/articlePrint.aspx?type=print&ID=43594
- Benedict A, Charbonneau C, Hidi J, et al: Economic evaluation of sunitinib, sorafenib, bevacizumab/interferon- α or temsirolimus in 1st-line treatment of metastatic renal cell carcinoma (mRCC): An indirect comparison. *J Clin Oncol* 26, 2008 (suppl; abstract 5048)
- Tappenden P, Jones R, Paisley S, et al: Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. *Health Technol Assess* 11:1-146, 2007
- Grothey A, Hedrick EE, Mass RD, et al: Response-independent survival benefit in metastatic colorectal cancer: A comparative analysis of N9741 and AVF2107. *J Clin Oncol* 26:183-189, 2008
- Soria JC, Massard C, Le Chevalier T, et al: Should progression-free survival be the primary measure of efficacy for advanced NSCLC therapy? *Ann Oncol* 21:2324-2332, 2010
- Edgerly M, Fojo T: Is there room for improvement in adverse event reporting in the era of targeted therapies? *J Natl Cancer Inst* 100:240-242, 2008
- Hillner BE, Smith TJ: Efficacy does not necessarily translate to cost-effectiveness: A case study in the challenges associated with 21st-century cancer drug pricing. *J Clin Oncol* 27:2111-2113, 2009
- Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 357:2666-2676, 2007
- Miles DW, Chan A, Dirix LY, et al: Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor 2-negative metastatic breast cancer. *J Clin Oncol* 28:3239-3247, 2010
- Robert NJ, Dieras V, Glaspy J, et al: RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol* 29:1252-1260, 2011
- Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell cancer. *N Engl J Med* 353:123-132, 2005
- Bradbury PA, Tu D, Seymour L, et al: Economic analysis: Randomized placebo-controlled clinical trial of erlotinib in advanced non-small cell lung cancer. *J Natl Cancer Inst* 102:298-306, 2010
- Hoos A, Parmiani G, Hege K, et al: Cancer Vaccine Clinical Trial Working Group. A clinical development paradigm for cancer vaccines and related biologics *J Immunother* 30:1-15, 2007
- Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 355:2542-2550, 2006
- Manegold C, von Pawel J, Zatloukal P, et al: BO17704 (AVAIL). A phase III randomized study of first-line bevacizumab combined with cisplatin/gemcitabine in chemotherapy-naïve patients with advanced recurrent non-squamous cell lung cancer (NSCLC). *Ann Oncol* 19:vii1-vii4, 2008 (suppl 8)
- Ranpura V, Hapani S, Wu S, et al: Treatment-related mortality with bevacizumab in cancer patients: A meta-analysis. *JAMA* 305:487-494, 2011
- Wacker B, Nagrani T, Weinberg J, et al: Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. *Clin Cancer Res* 13:3913-3921, 2007
- Wu S, Chen JJ, Kudelka A, et al: Incidence and risk of hypertension with Sorafenib in patients with cancer: A systematic review and meta-analysis. *Lancet Oncol* 9:117-123, 2008
- Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 350:2335-2342, 2004
- Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2-positive metastatic breast cancer that overexpresses HER2. *N Engl J Med* 144:788-792, 2001
- Santoro A, Gullo G: Trastuzumab beyond progression: A challenge to translational oncology? *Ann Oncol* 21:2131-2134, 2010

23. Montemurro F, Redana S, Geuna E, et al: Trastuzumab beyond progression in retrospective analysis: An issue of equal opportunities. *Oncologist* 16:534-536, 2011
24. Kaufman B, Mackey JR, Clemens MR, et al: Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2–positive, hormone receptor–positive metastatic breast cancer: Results from the randomized phase III TAnDEM study. *J Clin Oncol* 27:5529-5537, 2009
25. Davidoff AJ, Tang M, Seal B, et al: Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol* 28: 2191-2197, 2010
26. Wozniak AJ, Crowley JJ, Balcerzak SP, et al: Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell cancer: A Southwest Oncology Group study. *J Clin Oncol* 16:2459-2465, 1998
27. Pirker R, Szczesna A, von Pawel J, et al: A randomized multicenter phase III trial of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non-small lung cancer NSCLC (FLEX). *J Clin Oncol* 26 (May 20, Suppl 3), 2008
28. Pirker R: Results of phase III study of patients with stage IIb/IV disease and high epidermal growth factor receptor (EGFR) expression [FLEX]. Presented at the 14th World Conference on Lung Cancer, Amsterdam, the Netherlands, July 3-7, 2011 (abstr 1557)
29. Sandler A, Jing Yi, Dahlberg S, et al: Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/ carboplatin for advanced non-small cell lung cancer. *J Thor Oncol* 5:1416-1423, 2010
30. Nadler E, Yu E, Ravelo A, et al: Bevacizumab treatment to progression after chemotherapy: Outcome from a U.S. community practice network. *Oncologist* 16:486-496, 2011
31. Maemondo M, Inoue A, Kobayashi K, et al: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 362:2381-2388, 2010
32. Yang C-H, Fukuoka M, Mok TS, et al: Final overall survival (OS) results from a phase III, randomised, open-label, first-line study of gefitinib (G) v carboplatin/ paclitaxel (C/P) in clinically selected patients with advanced nonsmall cell lung cancer (NSCLC) in Asia (IPASS). Presented at the 35th European Society for Medical Oncology (ESMO) Congress, Milan, Italy, October 8-12, 2010 (abstr LBA2)
33. Chen G, Feng J, Liu Xq, et al: Efficacy results from the randomised phase III OPTIMAL (CTONG 0802) study comparing first-line erlotinib versus carboplatin (CBDCA) plus gemcitabine (GEM), in Chinese advanced non-small-cell lung cancer (NSCLC) patients (pts) with EGFR activating mutations. Presented at the 35th European Society for Medical Oncology (ESMO) Congress, Milan, Italy, October 8-12, 2010 (abstr LBA13)
34. 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 randomized, double blind, phase 3 study. *Lancet* 374: 1432-1439, 2009
35. Cappuzzo F, Ciuleanu T, Stelmakh L, et al: SATRUN: A double-blind randomized phase III study of maintenance erlotinib versus placebo following non-progression with first-line platinum-based chemotherapy in patients with advanced NSCLC. *J Clin Oncol* 27:407s, 2009 (suppl; abstr 8001)
36. Coudert B, Ciuleanu T, Park K, et al: Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. *Ann Oncol* [epub ahead of print on May 24, 2011]
37. Kelley RK, Venook AP: Nonadherence to imatinib during an economic downturn. *N Engl J Med* 363:596-598, 2010
38. Malin JL: Wrestling with the high price of cancer care: Should we control costs by individuals' ability to pay or society's willingness to pay? *J Clin Oncol* 28:3212-3213, 2010
39. Mason A, Drummond M, Ramsey S: Comparison of anticancer drugs coverage decisions in the United States and United Kingdom: Does the evidence support the rhetoric? *J Clin Oncol* 28:3234-3238, 2010
40. Fidias P, Novello S: Strategies for prolonged therapy in patients with advanced non-Small-Cell lung cancer. *J Clin Oncol* 28:5116-5123, 2010
41. Ellis LM, Haller DG: Bevacizumab beyond progression: Does it make sense? *J Clin Oncol* 26: 5313-5315, 2008
42. Grothey A, Surgue MM, Purdie DM, et al: Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: Results from a large observational cohort study (BRITE). *J Clin Oncol* 16:3212-3217, 2008
43. Grothey A: The role of chemotherapy in stage IV colorectal cancer: Focus on combinations with biological agents and conversion therapy. *Commun Oncol* 5:3-8, 2008
44. Karapetis CS, Khambata-Ford S, Derek DJ et al: K-ras Mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 359:1757-1765, 2008
45. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 350:2129-2139, 2004
46. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 361:947-957, 2009
47. Lopes G, Segel JE, Tan DSW, et al: Cost-effectiveness of epidermal growth factor receptor mutation testing and first-line treatment with gefitinib for patients with advanced adenocarcinoma of the lung. *Cancer* doi: 10.1002/cncr.26372
48. National Comprehensive Cancer Network: National Comprehensive Cancer Network guidelines for non-small cell lung cancer. www.nccn.org/professionals/physician_gls/f_guidelines.asp
49. Guirgis HM: A perspective on tyrosine kinase inhibitors in gastrointestinal stromal tumors and cancer: Past and present with emphasis on future and cost. *Cancer Therapy* 5:417-436, 2007
50. Twelves C, Cortes J, Vahdat LT et al: Phase III trials of eribulin mesylate (E7389) in extensively pretreated patients with locally recurrent or metastatic breast cancer *Clin Breast Cancer* 10:160-163, 2010
51. Reed SD, Li Y, Anstrom KJ, et al: Cost effectiveness of ixabepilone for metastatic breast carcinoma progressing after anthracycline and taxane treatment. *J Clin Oncol* 27:2185-2191, 2009
52. Thomas ES, Gomez HL, Li RK, et al: Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol* 25:5210-5217, 2007
53. McKee AE, Farrell AT, Pazdur R, et al: The role of the U.S Food and Drug Administration review process: Clinical trial endpoints in oncology. *Oncologist* 15:13-18, 2010 (suppl 1)
54. Ferrusi IL, Leighl NB, Kulin NA, et al: Do economic evaluations of targeted therapy provide support for decision makers? *J Oncol Pract* 7:36s-45s, 2011