Title

Five years of cancer drug approvals: Innovation, efficacy, and costs

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Authors

Mailankody, Sham

Prasad, Vinay

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Letters

RESEARCH LETTER

Five Years of Cancer Drug Approvals: Innovation, Efficacy, and Costs

The price of cancer drugs has risen, drawing criticism from leading academics.[1,2] The annual cost of a new cancer medication now routinely exceeds $100 000, and medical bills have become the single largest cause of personal bankruptcy.[2] Although some contend that the high cost of drugs is required to support re-search and development efforts,[3] the fact remains that when costs and revenues are balanced, the pharmaceutical industry generates high profit margins.[4]

High profits may be justified if novel products offer significant benefits to patients (thus producing indirect economic value through the patients' restored health) or if they represent significant pharmacologic advances over their predecessors—offering new mechanisms of actions and emblematic of high-risk research. We investigated whether novelty of medications or their relative benefits affected drug pricing.

Methods | We identified all oncologic drugs approved by the US Food and Drug Administration (FDA) between January 1, 2009, and December 31, 2013. Oncologic drugs were approved based

Table. Last 20 Oncologic Drugs Approved Between 2009 and 2013 by the US Food and Drug Administration

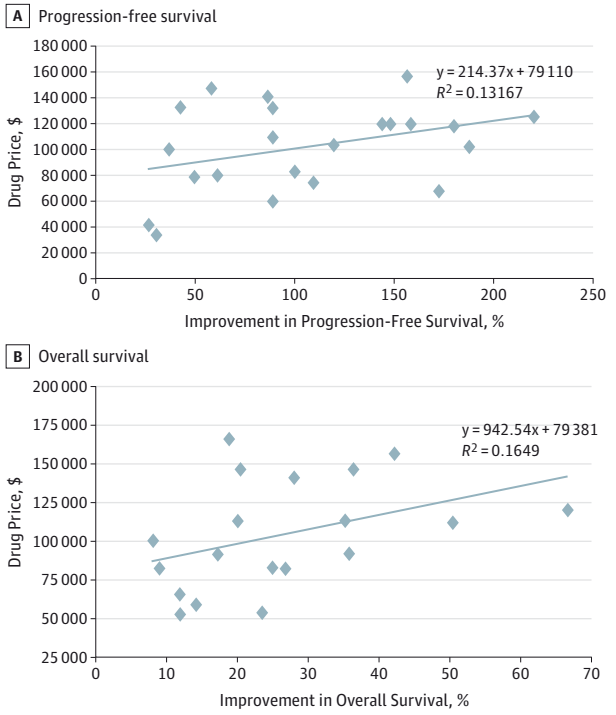
Drug and Indication	Cost per Year of Treatment, $[a]	Parent Drug	Mechanism of Action	Clinical Benefit
Sorafenib for papillary thyroid cancer	140 984	NA	First approved VEGFR and RAS tyrosine kinase inhibitor	Median PFS, 10.8 vs 5.8 mo
Crizotinib for non-small-cell lung cancer	156 544	NA	Anaplastic lymphoma kinase inhibitor	Median PFS, 7.7 vs 3.0 mo
Ibrutinib for mantle cell lymphoma	157 440	NA	Bruton tyrosine kinase inhibitor	RR, 66%; median DOR, 17.5 mo
Obinutuzumab for chronic lymphocytic leukemia	74 304	Rituximab	Anti-CD20 monoclonal antibody	Median PFS, 23.0 vs 11.1 mo
Pertuzumab for breast cancer	78 252	Trastuzumab	Anti-her2 monoclonal antibody	Pathologic CR, 39.3% vs 21.5%
Nab-paclitaxel[b] for pancreatic cancer	82 231	Paclitaxel	Albumin-bound paclitaxel (microtubule inhibitor)	Median OS, 8.5 vs 6.7 mo
Afatinib for non-small-cell lung cancer	79 920	Erlotinib	EGFR tyrosine kinase inhibitor	Median PFS, 11.1 vs 6.9 mo; median OS, NS
Lenalidomide for mantle-cell lymphoma	124 870	Thalidomide	Immunomodulatory drug (thalidomide analogue)	RR, 26%; median DOR, 16.6 mo
Trametinib for malignant melanoma	125 280	NA	First approved mek inhibitor	Median PFS, 4.8 vs 1.5 mo
Dabrefenib for malignant melanoma	109 440	Vemurafenib	BRAF inhibitor	Median PFS, 5.1 vs 2.7 mo; median OS, NS
Radium 223 for prostate cancer	82 800	NA	First approved radiotherapeutic drug	Median OS, 14.0 vs 11.2 mo
Erlotinib for non-small-cell lung cancer	82 827	NA	First approved EGFR tyrosine kinase inhibitor	Median PFS, 10.4 vs 5.2 mo; median OS, NS
Ado-trastuzumab emtansine for breast cancer	113 161	NA	First approved anti-her2 antibody drug conjugate	Median PFS, 9.6 vs 6.4 mo; median OS, 25.1 vs 20.9 mo
Pomalidomide for multiple myeloma	150 408	Thalidomide	Immunomodulatory drug (thalidomide analogue)	RR, 29%; median DOR, 7.4 mo
Bevacizumab for colorectal cancer	59 422	NA	First anti-VEGF monoclonal antibody	Median PFS, 5.7 vs 4 mo; median OS, 11.2 vs 9.8 mo
Ponatinib for chronic myeloid leukemia and Ph* acute lymphoblastic leukemia	137 952	Imatinib	Bcr-abl tyrosine kinase inhibitor	Major cytogenetic response, 54%; median DOR, 3.2-9.5 mo
Abiraterone for prostate cancer	92 092	Ketoconazole	Androgen biosynthesis inhibitor	Median OS, 35.3 vs 30.1 mo
Cabozantinib for medullary thyroid cancer	118 800	NA	First multikinase (including c-met and VEGF) inhibitor	Median PFS, 11.2 vs 4 mo; median OS, NS
Omacetaxine for chronic myeloid leukemia	168 366	Homoharringtonine	Protein translation inhibitor	Major cytogenetic response, 14.3%; median DOR, 12.5 mo
Nab-paclitaxel[b] for non-small-cell lung cancer	82 231	Paclitaxel	Albumin-bound paclitaxel (microtubule inhibitor)	RR, 33% vs 25%; median OS, NS
Regorafenib for colorectal cancer	141 372	Sorafenib	Multikinase inhibitor	Median PFS, 2 vs 1.7 mo; median OS, 6.4 vs 5 mo

Abbreviations: CR, complete response; DOR, duration of response; NA, not applicable; NS, not significant; OS, overall survival; PFS, progression-free survival; Ph*, Philadelphia chromosome positive; RR, response rate; UA, unavailable; (V)EGF(R), (vascular) endothelial cell growth factor (receptor).

[a] Average wholesale prices were obtained from Redbook online ([subscription required] http://www.redbook.com/redbook/online/).

[b] This drug was approved separately for 2 indications.

Figure. Linear Regression Analysis of Drug Price vs Percentage Improvement in Survival



Each point on the graphs represents 1 drug.

on improvements in overall survival (OS), disease response rate (RR) (eg, hematologic and/or tumor response) or progression- or disease-free survival (PFS) (eg, a delay in progression or relapse). The cost of a full course or 12 months of treatment was estimated from the average wholesale price obtained from the most recent edition of the Redbook online ([subscription required] http://www.redbook.com/redbook/online/). Each of us individually extracted the data, and then we compared results. Discrepancies were resolved by consensus.

Statistical analysis was performed using Stata software, version 13.0 (StataCorp LP). The Mann-Whitney and Kruskal-Wallis tests were used because data were not normally distributed. Linear regression was performed to ascertain relationships between continuous variables.

Results | From January 1, 2009, to December 31, 2013, the US FDA approved 51 drugs in oncology for 63 indications. During this time, 9 drugs received more than 1 approved indication. The **Table** lists the last 20 drugs (total of 21 approvals) approved by the FDA and their median wholesale prices.

Of these 51 drugs, 21 (41%) exert their effect via a novel mechanism of action, while 30 (59%) are next-in-class drugs. Among 63 unique indications for approval, 22 drugs (35%) were approved based on RRs, 22 (35%) based on PFS, and 19 (30%) based on OS. There was no difference in the median price per year of treatment between the 30 next-in-class drugs ($119 765) and the 21 novel drugs ($116 100) ($P$ = .42).

Drugs approved based on RR were priced highest, with median costs per year of treatment of $137 952. This was greater than the price of drugs approved on the basis of OS (median cost, $112 370) ($P$ = .004) and drugs approved on the basis of PFS (median cost, $102 677) ($P$ = .002). There was no significant difference in the price of drugs approved on the basis of OS or PFS (P = .62).

We evaluated for a relationship between the percentage improvement in PFS or OS and drug price (**Figure**). There was no significant relationship between cost and the percentage improvement in end point (PFS, β = 214.4; 95% CI, −42.4 to 471.1; P = .10; OS, β = 942.5; 95% CI, 143.0 to 2028.1; P = .09), and correlation coefficients were low (PFS, R^2 = 0.132; OS, R^2 = 0.165).

Discussion | Cancer drug prices are rising faster than the prices in other sectors of health care, drawing concern from patients, physicians, and policy researchers.[5,6] We found little difference in the median wholesale price of 21 novel drugs and 30 next-in-class drugs approved over a 5-year period (next-in-class drugs, $119 765; novel drugs, $116 100; P = .42). Our results suggest that the price of cancer drugs is independent of novelty. Additionally, we found little difference in price among drugs approved based on time-to-event end points and drugs approved on the basis of RR. Our results suggest that current pricing models are not rational but simply reflect what the market will bear.

Sham Mailankody, MB BS
Vinay Prasad, MD, MPH

Author Affiliations: Medical Oncology Service, National Cancer Institute, Bethesda, Maryland.

Corresponding Author: Vinay Prasad, MD, MPH, Medical Oncology Service, National Cancer Institute, National Institutes of Health, 10 Center Dr 10/12N226, Bethesda, MD 20892 (vinayak.prasad@nih.gov).

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Correction: This article was corrected on April 30, 2015, for an error in the Table. An incorrect indication was given for the drug ibrutinib; the correct indication is mantle cell lymphoma.

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