Editorial

Uncommon tumors and exceptional therapies: paradox or paradigm?

Fadi Braiteh and Razelle Kurzrock

Phase I Program, Division of Cancer Medicine, The University of Texas, M. D. Anderson Cancer Center, and the University of Texas Graduate School of Biomedical Sciences at Houston, Houston, Texas

Abstract

Why does it seem that, repeatedly, when a new treatment with a striking effect is discovered in the cancer field, it is effective for a very rare cancer type? For example, groundbreaking therapeutic discoveries have been made for extremely uncommon malignancies such as hairy cell leukemia, chronic myelogenous leukemia, seminoma, gastrointestinal stromal tumor, (del)5q myelodysplastic syndrome, and acute promyelocytic leukemia. In contrast, progress in the most common and most intensively studied tumors—lung, breast, prostate, and colon cancer—has been slow and incremental. We hypothesize that the reason for this phenomenon is that the pathophysiologic basis for a tumor being rare is one and the same as the reason that it may ultimately be so treatable. That is, if a cancer can be derived only via a single aberrant molecular genetic aberration, then it should be both rare and easily targeted by a molecular cancer therapeutic approach. If, on the other hand, many distinct pathways can lead to the development of a specific tumor type, it should occur much more commonly and be significantly more difficult to treat. The corollary to our hypothesis is the prediction that new therapies will continue to show their most salutary effects in rare cancers. Furthermore, only by stratifying the common tumors, especially when using targeted agents, into the molecular subsets of diseases that compose them are we likely to achieve a substantial effect in these disorders. [Mol Cancer Ther 2007;6(4):1175–9]

Currently, cancer is the second leading cause of death in the United States (1). Prostate, breast, lung, and colon cancers constitute more than half of the new cases of malignancies. These four malignant categories attract the major share of preclinical and clinical drug development research efforts, at least in part because of the financial incentive to address the most prevalent diseases. Yet, over the last three decades, remarkable progress has been made in the medical treatment of several of the rarest cancers, whereas only incremental therapeutic progress has occurred in the most common tumors.

Rare disorders are defined as those with a prevalence of <0.07% in the Unites States and <0.05% in Europe.[1] Because of their low prevalence, by definition, there is much less expectation that the cost of developing a drug will be recovered from sales. Further, patients with common cancers are more likely to be represented in clinical trials than patients with rare tumors. Research in uncommon cancers also suffers from relatively fewer trials devoted to them. Indeed, the Orphan Drug Act was introduced in 1982 because it was felt that government incentives, such as 7 years of exclusive marketing, were needed to encourage research efforts in rare diseases (2). It is therefore rational to assume that the most striking therapeutic successes would be in the most common diseases. However, this is not so. Indeed, the paradox of cancer research is that the most dramatic treatment discoveries cluster in some of the least common cancers.

Our definition of a dramatic medical discovery is one in which a relatively simple systemic treatment produces responses (often complete or near-complete remissions) and/or markedly improves survival (by several years) in the majority of patients with that cancer. Examples of such therapeutic advances in very rare cancers include cisplatinum for seminomas (3), imatinib mesylate in gastrointestinal stromal tumors (4–6) and chronic myelogenous leukemia (5, 7–9), and lenalidomide in del(5q) myelodysplastic syndrome (refs. 10, 11; Table 1; refs. 12–20). Further, several very rare tumors show marked responses to several drugs. For example, idarubicin, all-*trans* retinoic acid, and arsenic are each extremely effective as single agents for the treatment of acute promyelocytic leukemia (21–24). Hairy cell leukemia is a very rare malignancy (25, 26) that occurs in only ~600 new cases per year in the United States. There are now at least three treatments for hairy cell leukemia, each with striking therapeutic efficacy as monotherapy: IFN-α (27), 2-chlorodeoxyadenosine (19, 20, 28–31), and pentostatin (12, 16, 32, 33). In the meantime, whereas some therapeutic advances have occurred in more common cancers,

Received 10/31/06; revised 1/17/07; accepted 2/23/07.

Requests for reprints: Razelle Kurzrock, Phase I Program, Division of Cancer Medicine, M. D. Anderson Cancer Center, Unit 422, 1515 Holcombe Boulevard, Houston, TX 77030-4009. Phone: 713-794-1226; Fax: 713-745-2374. E-mail: rkurzroc@mdanderson.org

doi:10.1158/1535-7163.MCT-06-0674

[1] http://rarediseases.info.nih.gov/; accessed on 3-1-2006.

Table 1. Agents approved by the Food and Drug Administration between 1990 and 2005 with a response rate of >70%

Agent	Year	Cancer indication	Molecular hallmark	Reference
Pentostatin	1991	Hairy cell leukemia	Primary oncogenic event unknown	(12, 16, 17, 33)
Cladribine	1993			(19, 20, 30, 31)
Idarubicin	1990	Acute promyelocytic leukemia	PML/RAR-α protein	(13, 20, 22)
All-*trans* retinoic acid	1995			(14, 15, 23, 24)
Arsenic trioxide	2000			(21)
Imatinib mesylate	2001	Chronic myelogenous leukemia (chronic phase)	Bcr-Abl tyrosine kinase	(5, 7–9)
Imatinib mesylate	2002	Gastro-intestinal stromal tumor (GIST)	Activating mutation in *KIT* or *PDGFR-α* gene	(4, 5)
Lenalidomide	2005	del(5q31) myelodysplastic syndrome	Primary oncogenic event unknown	(10, 11)

Abbreviations: PML, promyelocytic leukemia; RAR-α, retinoic acid receptor α.

their effect is limited to smaller subsets of patients, less striking responses, and more modest extension of survival. For many patients, metastatic disease in these tumors remains difficult to treat and still portends a dismal prognosis.

We postulate that the advances in rare tumors are not simply a paradox but rather that these are physiologically preordained and therefore represent a paradigm for understanding responses in cancer and, hence, for future therapeutic research. Indeed, our hypothesis is that the physiologic basis for tumors being rare is one and the same as the reason that they are ultimately so treatable. That is, these cancers are driven by a single aberrant mechanism, such as a single gene anomaly (Table 1; ref. 5). If a particular cancer can develop as a result of only a single, specific molecular abnormality, it is likely to be rare, and it is also more likely that therapy that effectively targets this aberration will have a significant effect on the majority of patients. On the other hand, if numerous distinct molecular defects can result in a certain type of tumor, as is likely in lung, colon, prostate, or breast cancer, then that type of tumor should occur commonly; at the same time, it is unlikely that a single, relatively simple therapy will have a dramatic effect on most of the patients being treated.

Between 1990 and 2005, the Food and Drug Administration in the United States approved 51 claims for new

Table 2. Agents approved, the initial cancer approval, average response rate, and success rate (SS = $n / N \times 1{,}000$)

	Estimated no. of new cases for year 2005	No. of new agents approved by the FDA between 1990–2005	SS = $n / N \times 1{,}000$	Average response rate to the newly approved agents
Prostate	232,090	0	0.00	00.0
Breast	212,930	6	0.03	30.0
Lung	172,570	3	0.03	20.0
Colorectal	145,290	3	0.02	36.8
Bladder	63,210	2	0.03	39.0
Melanoma	59,580	1	0.02	N/A
NHL	56,390	4	0.07	50.6
Kidney	36,160	2	0.06	17.0
Pancreas	32,180	1	0.03	08.0
Ovary	22,220	3	0.14	22.2
Brain tumor	18,500	1	0.05	23.0
Multiple myeloma	15,980	1	0.06	36.5
Myelodysplastic syndrome	15,000	2	0.13	78.0
Acute myeloid leukemia	11,960	1	0.08	75.0
Chronic lymphoblastic leukemia	9,730	2	0.21	56.2
Chronic myeloid leukemia	4,600	3	0.65	86.0
Acute lymphoblastic leukemia	3,970	4	1.00	51.2
Mesothelioma	1,776	1	0.56	51.2
Kaposi sarcoma	1,729	3	1.76	41.0
Cutaneous T-cell lymphoma	1,260	3	2.31	45.0
Acute promyelocytic leukemia	1,000	3	3.00	87.3
Hairy cell leukemia	500	2	4.00	87.0
Total	N/A	51	N/A	N/A

Abbreviations: FDA, Food and Drug Administration; NHL, non-Hodgkin's lymphoma.

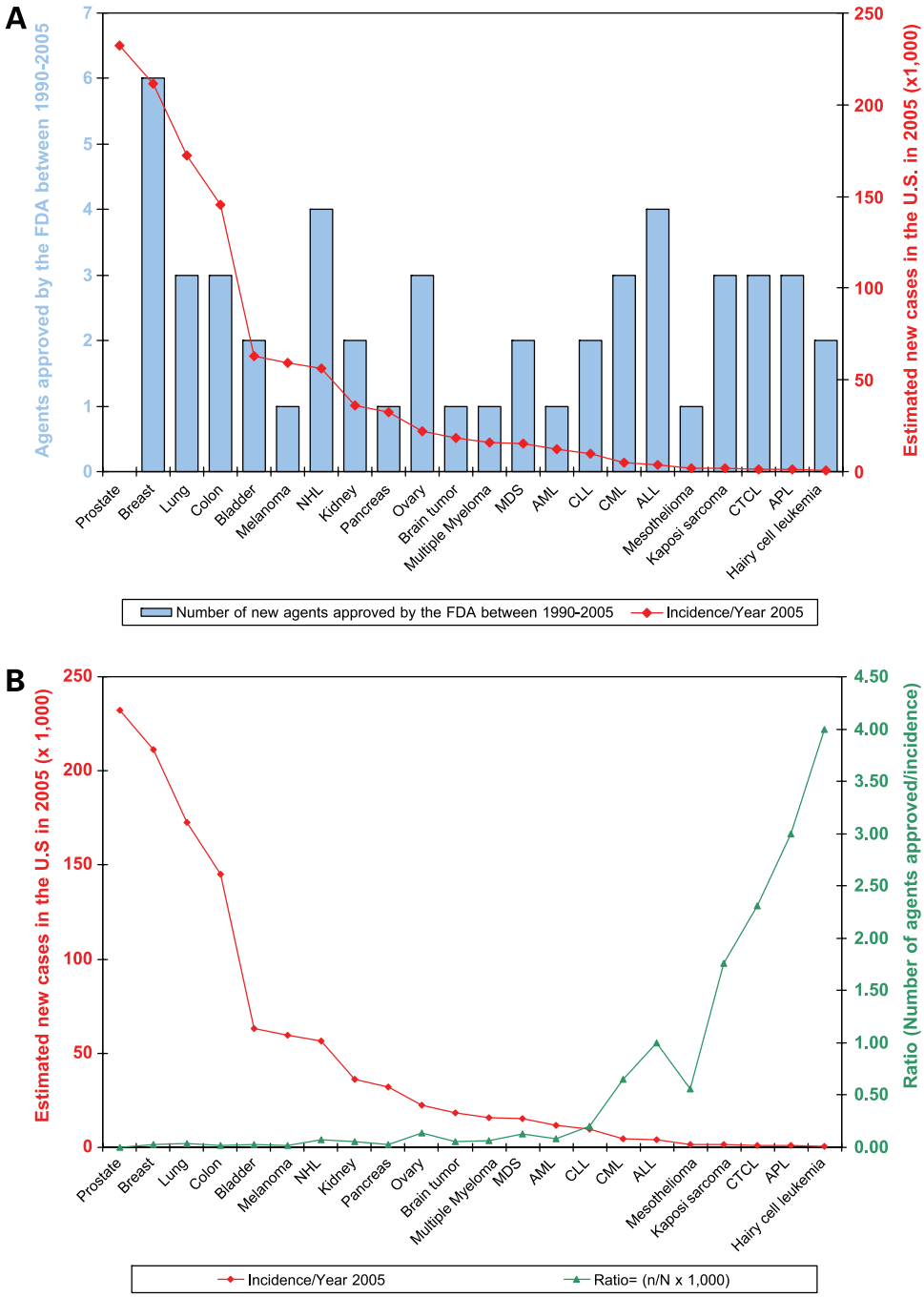

Figure 1. **A,** a review of all the new agents approved for the first time by the Food and Drug Administration between 1990 and 2005 and their initial indication. We excluded hormonal therapy agents, supportive therapy drugs, and newer indications for previously approved agents. We identified 51 agents approved for 21 different cancers. Additionally, we plotted in red the estimated incidence of these 21 cancers in the United States for the year 2005, in the order of from the most to the least frequent (1). This figure illustrates the disproportionately high number of agents approved for rare cancers compared with the most common types. **B,** calculation for each of the 21 cancer categories of the success rate SS as the ratio of the number (n) of new agents approved for that cancer over the number (N) of estimated new cases in the United States in 2005 ($SS = n / N \times 1{,}000$). The ratio is inversely proportional to the incidence of cancers, showing an inverse relationship between the number of drugs approved and the incidence of that cancer (a mirror image) with a strong Spearman rank correlation test ($R's = -0.94$, $P < 0.05$).

antineoplastic drugs (small molecules, antibodies, or cytotoxic), of which only 12 (21%) were initially indicated for the treatment of one of the four leading cancers (Table 2).[2] The majority of new treatments were, however, approved for rare or very rare tumors (Fig. 1A and B). The introduction in 1982 of the Orphan Drug Act could have facilitated the emergence of some of these drugs, but would not account for their predominance (34). Furthermore, the response rates for agents eventually approved were generally in the 5% to 40% range for common cancers, but were much higher for rare tumors (Fig. 2), easily exceeding 70% for some of them (Table 1). It could be argued that because of the small number of patients available to be enrolled in clinical trials of orphan drugs, only new treatments with a very high efficacy would successfully show a statistically significant benefit adequately to allow their approval. However, this does not

[2] http://www.fda.gov/cder/cancer/approved.htm; accessed on 3-2-2006.

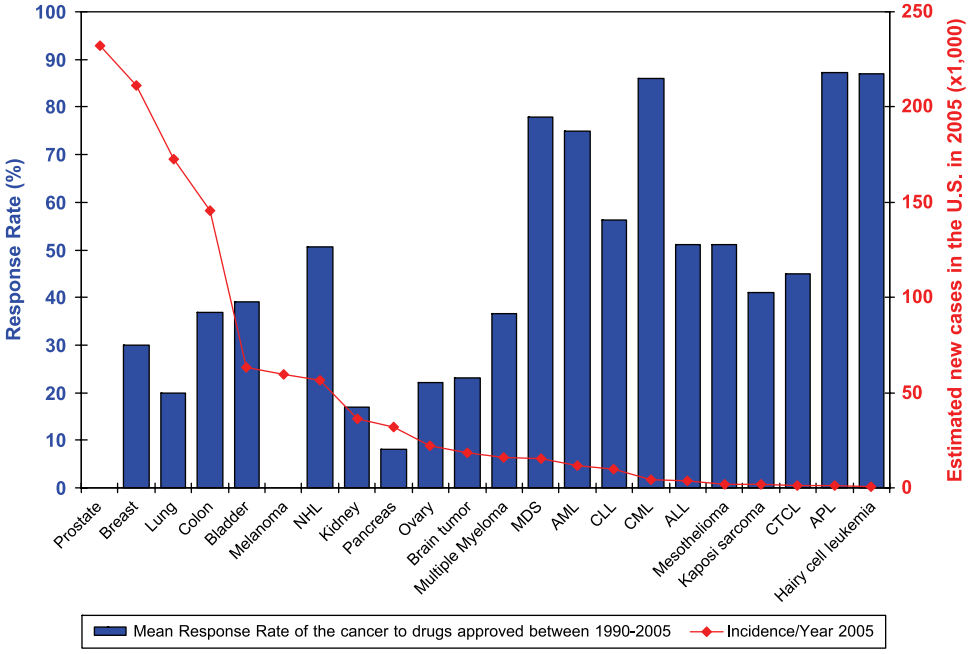

Figure 2. Using the same 51 identified Food and Drug Administration–approved agents over the period 1990 to 2005, we calculated the average individual response rates for each cancer, the mean of response rates of all new agents approved for that particular malignancy.

explain why so many successful compounds cluster in the rare or very rare cancers.

Although superficially it may seem that common tumors will remain difficult to treat, our hypothesis, in fact, has a more important therapeutic research implication. That is, it is likely that common tumors are composed of numerous distinct ''molecular'' subsets of disease, and therapy that yields a robust response in a small percentage of patients (e.g., 2–10%) should not be abandoned, as has previously happened. Nor should a randomized survival study of the entire population of patients take place because an unselected group would almost certainly obscure the responsive subset, unless there were thousands of participants. Research investigators should be redirected to an intense effort to identify the molecular characteristics that are the hallmark of the responders. A recent example that highlights this issue involves epidermal growth factor receptor (EGFR) inhibitors. Gefitinib (35) and erlotinib (36) induce responses in about 10% (8.9% and 12%, respectively) of all enrolled patients with advanced non–small cell lung cancer. Yet, in patients not selected based on their *EGFR* mutation status, gefitinib provided no survival advantage despite remarkable salutary effects in some patients (37). More recently, it has been shown that the response to gefitinib (38) and the sensitivity to erlotinib (39) in patients with non–small cell lung cancer are pronounced in those individuals whose tumors bear mutations in the tyrosine-kinase domain of the *EGFR* gene (which occurs in ~10% of the lung cancer population; refs. 40–44).

Our hypothesis therefore suggests that the current strategy of treating entire populations of patients with what we think is a single tumor type in a similar fashion and abandoning therapy because of low response rate will continue to yield slow progress in cancer drug development. If the expectation that highly effective therapies will affect only small subsets of patients is accepted, a paradigm shift toward intense studies of these subsets, or indeed more personalized therapy, will be important if we are to make leaps, rather than small steps, in the field of molecular cancer therapeutics.

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Mol Cancer Ther 2007;6:1175-1179.