

PERSPECTIVE

Revoking the Privilege: Targeting HER2 in the Central Nervous System

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ABSTRACT

Pharmacologic agents developed for cancer therapy have traditionally relied on a therapeutic ratio of effects between tumors and normal tissue. Over the past decade, this concept has been refined through the development of agents that are intended to specifically target tumor cells. The epidermal growth factor receptor (EGFR) (ErbB) family of receptor tyrosine kinases is an intensely studied target in many cancer cell types, and several successful therapeutic agents have been developed to block the growth promoting functions of these receptors. However, with their success has come the evolution of novel clinical scenarios by which tumor cells can evade these targeted therapies. Trastuzumab, a monoclonal antibody to

Her2/ErbB2 that is used in breast cancer, has been shown to provide a survival benefit for patients whose tumors express this receptor but it does not have activity in the central nervous system because of the blood-brain barrier. In this issue of *Molecular Pharmacology*, Emanuel et al. (p. 328) report on a tyrosine kinase inhibitor that targets Her2/neu and also crosses the blood-brain barrier. Efforts to improve current strategies of targeting this receptor may lead not only to benefits in the treatment of breast cancer but also to advances in the treatment of other central nervous system malignancies, such as gliomas and medulloblastoma.

In 1906, speaking about the treatment of bacterial pathogens, Paul Ehrlich remarked that it would “be easy to effect a cure if substances have been discovered which have a specific affinity for these bacteria and act . . . on these alone, while they possess no affinity for the normal constituents of the body. Such substances would then be magic bullets.” Ehrlich’s scientific work was subsequently awarded the Nobel Prize in 1908. With the advent of molecularly targeted therapies in oncology has come the promise of “magic bullets” in the treatment of malignancy. We now have agents that enable disease specific treatment with reduced normal tissue toxicity. However, as more and more molecularly targeted agents enter clinical evaluation, we are seeing that finding a magic bullet does indeed take a certain amount of magic. The utility of a targeted agent within a patient population will depend upon the appropriate answers to a number of questions. First, is the molecular target present within the tu-

mor? Second, can one “hit” the target with the agent of interest? Third, is there some clinically meaningful endpoint as a result of the specific inhibition of the target in this disease?

In the case of imatinib (Gleevec), the initial results were resoundingly “yes” on all counts. The BCR-ABL tyrosine kinase was present and active in virtually all chronic myeloid leukemia cells, the tyrosine kinase was accessible and specifically inhibited by the drug, and clinical remissions were observed in 50% of patients using a single-agent even when in blast crisis (Druker et al., 2001a,b). It was truly a remarkable achievement that would have made Ehrlich proud! Initial enthusiasm for gefitinib for the treatment of non-small-cell lung cancer was also high given that 40 to 80% of non-small-cell lung cancers overexpress EGFR (the target for gefitinib and erlotinib), and dramatic responses were observed in animal models and initial clinical studies (Kris et al., 2003). Only later was it determined that EGFR was present, biologically active, and critical in only a subset of patients, thus yielding responses in a small number of patients (often 10–20%) with no response in the bulk of the

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ABBREVIATIONS: EGFR, epidermal growth factor receptor; CNS, central nervous system; RTK, receptor tyrosine kinases.

remainder (Lynch et al., 2004). Here was an example of the target's presence in only a fraction of all patients and being biologically relevant in an even smaller population. Therefore, applying the "rules" described above, one could clearly find a population of patients who express the target and one might even be able to block its activity; however, the impact of this inhibition may or may not have clinical relevance. The magic in this case is deciding exactly who will benefit from this particular bullet (Sordella et al., 2004).

For trastuzumab (Herceptin) in the treatment of Her2/neu positive breast cancer, another twist has appeared in the interplay between biologic characteristics of the cancer and pharmacokinetics of the therapeutic agent. Results to date have been particularly encouraging with trastuzumab Her2/neu is clearly overexpressed and plays a significant role in a sizable population of patients with breast cancer. In addition, treatment with trastuzumab inhibits the activity of this critical pathway, resulting in clinically astounding improvements in disease-free and overall survival (Piccart-Gebhart et al., 2005; Romond et al., 2005). However, only as time has passed have we begun to observe the limitations in this particular targeted agent. The first hint of the treatment hitting more than the targeted cells was focused on the presence of Her2/neu in cardiac myocytes and the resulting decrease in cardiac function, particularly when combined with anthracyclines. With time, it appears that this limitation may not be as concerning as was once thought (Ewer et al., 2005; Bria et al., 2008). Now, however, a new clinical limitation has been observed with a sizable portion of women with Her2/neu positive breast cancer who are otherwise free of disease. These women now present with metastatic disease to the brain (Piccart-Gebhart et al., 2005; Romond et al., 2005; Bria et al., 2008), a "sanctuary" or "privileged" site from many systemic therapies. Falling back again to the guidelines described above, we can see that although present and biologically active Her2/neu may not always be "hit" by trastuzumab. In this case, the very nature of the agent as an antibody (see Fig. 1), with high molecular weight, enables high selectivity for Her2/neu but also limits its penetration past the blood-brain barrier. (Coincidentally, Ehrlich made the first observations of the existence of the blood-brain barrier.) This inability to target tumor cells isolated in the CNS has presumably led to the newly identified clinical phenomena in which women with Her2/neu-positive disease are relapsing only in the CNS after trastuzumab treatment, a change in the natural history of breast cancer.

In this issue of *Molecular Pharmacology*, Emanuel et al. (2008) have identified a novel compound (JNJ-2871063) that

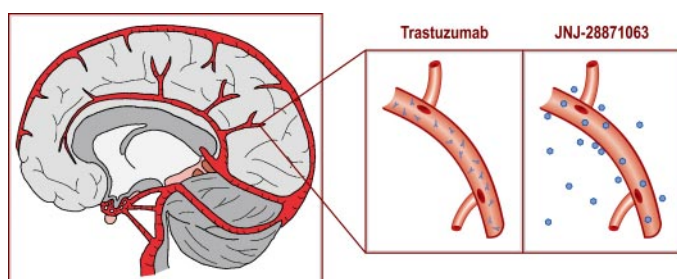


Fig. 1. CNS penetration of monoclonal antibodies versus small molecule inhibitors

is an inhibitor of the ErbB family of receptor tyrosine kinases (including ErbB2, which is also known as Her2/neu). In this study, the investigators analyzed kinase activity, receptor phosphorylation status, and results from high-throughput kinase profiling to demonstrate the specificity and effectiveness of this new compound on the ErbB2 receptor family. The comparisons made between the JNJ compound and other ErbB RTK inhibitors underscore the fact that in general, tyrosine kinase inhibitors have multiple targets and cellular effects that are unpredictable and thus require empiric demonstration of efficacy in the clinical setting. Yet the study presented by Emanuel et al. (2008) suggests that if the ErbB RTK family is the target for anticancer therapy, then this compound may have both enhanced selectivity and efficacy compared with previous small-molecule RTK inhibitors. The second notable finding about JNJ-2871063 is its activity in the central nervous system, a site privileged from trastuzumab and possibly other small-molecule inhibitors. Either oral or intravenous administration of the JNJ compound to mice bearing tumors demonstrated that the drug penetrates both the tumor microenvironment as well as the blood-brain barrier. Subsequent experiments in a mouse intracranial tumor model demonstrated significant extension of survival in mice treated with this compound. These findings provide some hope for clinical development of an agent to treat CNS metastasis of Her2/neu-positive breast cancer. With a little magic, there may even be a success in treating or delaying the appearance of this unique clinical niche. However, the ability to target Her2/neu in the CNS would certainly not be limited to breast cancer. Clinical trials of gefitinib and erlotinib for newly diagnosed or recurrent glioblastoma have already been performed with somewhat disappointing results (Rich et al., 2004; Haas-Kogan et al., 2005; Chakravarti et al., 2006; Krishnan et al., 2006). However, like many malignant cell types, gliomas express multiple ErbB RTK family members, each of which provides parallel proliferative and survival signals. Thus, a pharmacologic agent that has enhanced activity against Her2/neu may improve responses in this disease as well.

In addition, such an agent might open the door to the treatment of another compelling clinical need, medulloblastoma, the most frequent malignant pediatric brain tumor. At present, treatment of medulloblastoma typically involves surgical excision followed by radiation therapy to the brain and spine and systemic chemotherapy. With this treatment, overall prognosis for patients is excellent (with event-free survival of ~85% at 5 years for patients with standard-risk disease), but long-term toxicity can be severe; therefore, improvements certainly could be made in the therapeutic index. A number of risk factors have been identified that portend a more aggressive clinical behavior in patients with medulloblastoma (Polkinghorn and Tarbell, 2007). It is noteworthy that Her2/neu is amplified and overexpressed in a sizeable subpopulation of patients with medulloblastoma (Tong et al., 2004), and retrospective reviews have suggested that its expression is correlated with worse progression-free and overall survival (Gilbertson et al., 1992, 1995; Herms et al., 1997). In preclinical models, overexpression of Her2/neu in a medulloblastoma cell-line resulted in increased expression of genes associated with a metastatic phenotype and increased invasion (Hernan et al., 2003). Currently, Her2/neu expression and its impact upon patient outcome is being prospectively analyzed in a series of multi-institutional trials; if its prog-

nostic value is borne out, then an ErbB-specific agent with good CNS penetration (such as JNJ-2871063) would satisfy the first two of the guidelines above. Therefore, it would not be unreasonable to evaluate whether the addition of an ErbB2 inhibitor to conventional treatment might increase disease control and/or decrease the toxicity associated with the treatment of medulloblastoma.

Near the turn of the 20th century, the German scientist Paul Ehrlich envisioned a series of specific chemical agents or “magic bullets” as treatment for bacterial pathogens, a concept that guided his investigations of chemotherapeutic drugs later in his career. A scientist and clinician, Ehrlich was cognizant of the long time necessary to develop any clinical agent, remarking on his own efforts to develop a chemotherapy that “many year(s) . . . must elapse before a drug can be perfected which can even be tried on human beings.” Now, more than 100 years later, we continue to struggle with the issues that plagued Ehrlich as well as additional ones. Is the target present? Can we hit it? And what is the clinical effect? These questions are now accompanied by a fourth: How will tumor cells adapt to the targeted therapy? Although multiple small-molecule RTK inhibitors have been developed for groups or families of RTKs, this strategy for targeting tumor cells has had its share of failures as well as successes, and just as Ehrlich foresaw, the true applicability of these agents will require much further pre-clinical and clinical evaluation.

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