Biologically Targeted Cancer Therapy and Marginal Benefits: Are We Making Too Much of Too Little or Are We Achieving Too Little by Giving Too Much?

Tito Fojo and David R. Parkinson

Abstract

We describe the development and approval of biologically targeted agents in the clinic through examples chosen from the experience with inhibitors of the epidermal growth factor (EGF) and VEGF pathways. Despite extensive biological rationale for the use of these classes of molecules, marginal clinical benefits have been observed in broad patient populations, and the agents have entered into general clinical practice. We discuss why this situation is unsatisfactory because marginal general benefit may often be at the expense of toxicity to nonbenefiting or even harmed patients. Finally, we point out that emerging technologies bring the promise of allowing the identification of patients who might potentially benefit from a therapy. However, development of this technology will not move forward without broader recognition of its need by the range of stakeholders, including patients, advocates, academic and private oncologists, drug sponsors, and those who develop drugs and diagnostic tests.

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It is a truism that many cancer therapeutics provide marginal benefits to the majority of patients to whom they are administered. Increasingly, the advances observed in the clinical trials that form the basis of approval do not translate into a statistical or meaningful overall survival (OS) benefit. The justification for regulatory approvals and introduction into broad clinical practice includes the arguments that survival benefit was obscured by subsequent therapies or that the delay in the time to progression is itself of benefit to the patient. An alternative argument is that individual patients are indeed benefiting, and that the marginal benefits in the overall patient population represent our inability to identify these individuals.

In this article, we explore these issues from the perspective of biologically targeted therapies, the basis of the majority of current oncology drug development. The biological revolution has presented us with a plethora of targets for cancer therapy, and advances have made most of these targets "druggable." As a result, hundreds of relatively specific drugs are in development and a select few have been approved. Individual patients clearly are benefiting, yet results from large randomized trials are often disappointing. We discuss some examples of targeted therapies applied to common malignancies. The examples are disappointing, if for no other reason that such enormous application of resources, driven by advances in technology and our understanding of tumor biology, has, to date, had minimal impact on the common tumors. We also consider the likelihood that although some patients are benefiting, others may be harmed. We argue for refocusing our development strategy, with more resources allocated to accurate biological characterization of the tumors we are treating, linking this information closely to the effects of treatment and the clinical outcome.

The Gleevec Paradigm Meets the Reality of Biologically Complex Solid Tumors

Ten years into the targeted therapy revolution, the Gleevec paradigm seems to be the exception rather than the rule (1–3). In chronic myelogenous leukemia, a combination of a genetically simple disease "addicted" to a single pathway and a specific, relatively nontoxic drug generated much deserved enthusiasm a decade ago. Unfortunately, the road we have traveled with other tumors since identifying Gleevec as an active agent in chronic myelogenous leukemia has been less successful. Studies suggest extensive biological complexity within the historic classifications of colon, breast, and pancreatic cancer as well as high-grade glioblastoma, a complexity far greater than our most pessimistic original expectations (4–7). We also discovered that targeting widely expressed kinases in broad patient populations resulted in modest response rates, marginal changes in natural history, and carried the risks of a myriad of toxicities, the majority of which, although not lethal, manifest as chronic toxicities that may impact life (8–10).

This problem of therapies with marginal benefits and the "negative balance" one may achieve on the "ledger sheet" because of toxicity lead us to conclude that we are both
making too much of too little and achieving too little by giving too much. We propose that technology is at hand that can shift the balance on the “ledger sheet,” and that only a codevelopment strategy that identifies and treats only vulnerable tumors will be defensible going forward. The time has come for the era of personalized medicine to become a reality. Development strategies that administer therapies to populations that are not selected or are selected with methodologies not validated, or have little if any value, must become a strategy of the past.

Marginal Benefits: Examples from Agents Targeting the Epidermal Growth Factor Receptor Pathway

The acceptance of marginal therapies has received support from unlikely sources. In 2008, for example, the FLEX trial comparing vinorelbine plus cisplatin to the same combination with cetuximab as first-line treatment for advanced non–small cell lung carcinoma (NSCLC) was showcased at the American Society of Clinical Oncology (ASCO) plenary session (11). On the basis of a 1.2-month survival benefit, the authors concluded the “addition of cetuximab to platinum-based chemotherapy represents a new treatment option for patients with advanced non–small cell lung cancer.” Grade 1-2 toxicities, often chronic and responsible for adversely affecting the quality of a patient’s life, were not reported at the plenary session or in the subsequent Lancet publication (12). However, grade 3-4 toxicities, often the tip of the “toxicity iceberg,” were tabulated and found to be significantly greater. Leucopenia, febrile neutropenia, acne-like rash, diarrhea, and sepsis, for example, were found in 25, 22, 10, 5, and 2% of patients, respectively. In addition to its toxicity price, this "new treatment option," with a P-value (0.044) that barely achieved statistical significance, came at a cost exceeding $70,000 per patient. The ASCO press briefing asserted “these findings are likely to have a significant impact on the care of patients with these types of cancer” (emphasis added; ref. 13); and the ASCO Clinical Practice Guideline update on chemotherapy for stage IV NSCLC eventually ratified this option (14).

Unfortunately, the example of cetuximab in NSCLC is not unique, because clinical trials with marginal benefits abound. For example, The New England Journal of Medicine published the U.S. Food and Drug Administration (FDA) approved cetuximab for advanced colorectal cancer after it was shown to “prolong” OS by a statistically insignificant 1.7 months (P = 0.48) in combination with irinotecan, compared with single agent cetuximab, although not to the arguably more appropriate comparator, single agent irinotecan (15, 16). In its approval, the FDA noted differences in response rates and progression-free survival (PFS), but ignored the lack of OS differences. This minimal advance presaged the limited benefit of this and similar therapies in the front-line setting (17–19).

But marginal benefits from agents targeting the epidermal growth factor receptor (EGFR) pathway have not been confined to biologic agents. In pancreatic cancer, the addition of erlotinib to gemcitabine improved OS a mere 10 days (median 6.24 versus 5.91 months), despite “objective response rates that were not significantly different between the arms…” and higher frequencies of grade 1 or 2 rash, diarrhea, infection, and stomatitis, albeit with erlotinib dose reductions in 16% of patients and treatment discontinuation in 18% of patients (9). Yet, the FDA approved this marginal therapy for this difficult-to-treat disease (20). Numerous other examples can be cited, including combinations in which harm has occurred with significantly shorter PFS, increased toxicity, and inferior quality of life (21, 22).

Marginal Benefits: Examples from Agents Targeting the VEGF Receptor Pathway

Similar examples can be found when one examines agents targeting the VEGF receptor (VEGFR) pathway. For example, the FDA approved bevacizumab (avastin) in combination with paclitaxel (taxol) for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer (23). Initially granted accelerated approval for this indication, the use of bevacizumab now finds itself under the weight of emerging evidence that is equally marginal or worse and at risk for losing this indication. The initial approval for bevacizumab in combination with paclitaxel in breast cancer was based on data from the E2100 trial, also published in The New England Journal of Medicine, showing a 5.9-month prolongation of PFS without a prolongation of OS (24). This finding was “confirmed” by similar data that were not deemed “as robust” in other trials in breast cancer (25–28). As in the E2100 trial, statistically significant increases in PFS were recorded; however, as in the E2100 trial, there was no significant difference in OS, a secondary endpoint deemed a “challenge.”

Similar circumstances can be found with bevacizumab in NSCLC. ASCO highlighted, in its 2005 plenary session, and the FDA subsequently approved the use of bevacizumab in combination with carboplatin-paclitaxel for first-line treatment of “eligible patients” with locally advanced, recurrent, or metastatic nonsquamous NSCLC, on the basis of an OS increase of 2 months observed in the E4599 clinical trial (29–32). The addition of bevacizumab to chemotherapy quickly became standard for NSCLC in the United States, despite disagreement about the actual benefit and data that showed a cisplatin combination regimen without bevacizumab more effective and unequivocally not more toxic (Fig. 1; Tables 1 and 2; ref. 33). The latter observation emerged from the AVAiL trial examining the efficacy of bevacizumab when combined with cisplatin plus gemcitabine (33). In a similar patient population to that in E4599, the data showed a longer OS without bevacizumab, possibly attributable to the use of a cisplatin instead of carboplatin doublet. As in many clinical trials, the investigators conducting the
AVAiL trial concluded that the "PFS benefit did not translate into a significant OS benefit, possibly due to the high use of efficacious second-line therapies." This excuse, often advanced to explain why OS values are not statistically different, is not supported by the data in Tables 1 and 2 showing poststudy therapy was identical in both arms. Indeed, because patients randomized to placebo did not have an inferior OS and did not receive bevacizumab, one could conclude the addition of bevacizumab does not confer any benefit over conventional chemotherapies. Also note that the Δ PFS and Δ OS are essentially identical, within 0.1 month or 3 days of each other, arguing against the "loss of a PFS benefit," another frequent allegation whose origin is explained graphically in Fig. 1.

Marginal Benefit: How Much of a Benefit and Are We Ignoring Risks?

In all of these cases, we must ask ourselves if these marginal differences represent a benefit to patients with cancer. Our answer would be a qualified no, with respect to the overall populations of unselected patients receiving these therapies. Although we recognize the plight of patients suffering from an incurable cancer, and the value many
would place on an additional month or two of life, in an increasing number of cases, the average patient’s OS is, in fact, not improved. In these cases, support for such a therapy is, in our opinion, not warranted, albeit with possible exceptions. Certainly, such therapies do not deserve support when the costs are exorbitant and the benefits, if any, marginal or negative, except to an unrecognized subgroup of patients (Table 3). Although many have argued that delaying progression is of value even if it does not increase OS, we would argue that routinely administering therapy that does not improve OS and that may adversely affect quality of life is not defensible in the majority of cases (34, 35). PFS is not a surrogate for the onset of symptoms. The majority of patients on clinical trials are asymptomatic both at enrollment and when they experience official clinical trial–defined “disease progression” as evidenced, for

Table 3. Estimates of Drug Costs According to Quality-Adjusted Life Years (QALYs) for Regimens Discussed in Text

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Regimen</th>
<th>Dose ( ^c )</th>
<th>PFS or time on therapy</th>
<th>Amount needed ( ^d )</th>
<th>Cost/ mg or cost/ tablet</th>
<th>Total Cost</th>
<th>Increase in OS ( ^f )</th>
<th>Cost per QALY ( ^g )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin(^3))</td>
<td>NSCLC</td>
<td>(ref. 33)</td>
<td>15 mg/kg q 21 days</td>
<td>900 mg every 21 days</td>
<td>5 cycles(^T)</td>
<td>4500 mg $67/mg</td>
<td>$301,500</td>
<td>0.3 mos(^m)</td>
<td>$1,206,000</td>
</tr>
<tr>
<td>Erlotinib (Tarceva(^3))</td>
<td>Pancreatic cancer</td>
<td>(ref. 9)</td>
<td>150 mg daily</td>
<td>150 mg/day</td>
<td>3.75 mos(^T)</td>
<td>114 tablets $160/mg/tablet</td>
<td>$18,327</td>
<td>0.33 mos</td>
<td>$659,772</td>
</tr>
<tr>
<td>Bevacizumab (Avastin(^3))</td>
<td>Breast cancer</td>
<td>(ref. 24)</td>
<td>10 mg/kg q 14 days</td>
<td>600 mg every 14 days</td>
<td>7.1 months(^T)</td>
<td>9255 mg $67/mg</td>
<td>$62,009</td>
<td>1.5 mos(^m)</td>
<td>$496,072</td>
</tr>
<tr>
<td>Bevacizumab (Avastin(^3))</td>
<td>NSCLC</td>
<td>(ref. 33)</td>
<td>7.5 mg/kg q 21 days</td>
<td>450 mg every 21 days</td>
<td>6 cycles(^T)</td>
<td>2700 mg $67/mg</td>
<td>$18,090</td>
<td>0.5 mos(^m)</td>
<td>$434,160</td>
</tr>
<tr>
<td>Cetuximab (Erbitux(^3))</td>
<td>NSCLC</td>
<td>(ref. 12)</td>
<td>Loading: 400 mg/m(^2)</td>
<td>M: 250 mg/m(^2)/wk</td>
<td>18 wks(^T)</td>
<td>6975 mg $57/mg</td>
<td>$40,176</td>
<td>1.2 mos</td>
<td>$401,760</td>
</tr>
<tr>
<td>Cetuximab (Erbitux(^3))</td>
<td>CRC</td>
<td>(ref. 15)</td>
<td>Loading: 400 mg/m(^2)</td>
<td>M: 250 mg/m(^2)/wk</td>
<td>18 weeks(^K)</td>
<td>6975 mg $57/mg</td>
<td>$40,176</td>
<td>1.7 mos(^m)</td>
<td>$283,595</td>
</tr>
<tr>
<td>Cetuximab (Erbitux(^3))</td>
<td>NSCLC</td>
<td>(ref. 50)</td>
<td>Loading: 400 mg/m(^2)</td>
<td>M: 250 mg/m(^2)/wk</td>
<td>13 wks(^T)</td>
<td>5100 mg $57/mg</td>
<td>$29,376</td>
<td>1.3 mos(^m)</td>
<td>$271,163</td>
</tr>
<tr>
<td>Bevacizumab (Avastin(^3))</td>
<td>NSCLC</td>
<td>(ref. 32)</td>
<td>15 mg/kg q 21 days</td>
<td>900 mg every 21 days</td>
<td>7 cycles(^T)</td>
<td>6300 mg $67/mg</td>
<td>$42,210</td>
<td>2 mos</td>
<td>$253,260</td>
</tr>
</tbody>
</table>

\(^a\)Source of average wholesale prices (AWP’s) was Amerisource Bergen’s listing which is referenced as the “BlueBook AWP” from First DataBank.

\(^b\)NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; HCC = hepatocellular carcinoma.

\(^c\)Calculated for a 60 kg / 1.5 m\(^2\) patient.

\(^d\)Superscript \(^T\) refers to time of therapy as indicated in reference; superscript \(^P\) refers to time to progression, assumed for an oral therapy to be equal to time patient took medication.

\(^e\)For the regimen cited, administered as in the study cited, for the time report indicated therapy was administered or until the time of median disease progression as reported in the published study.

\(^f\)OS = Overall survival for the reference cited.

\(^m\)NS = not statistically significant; note that since by definition these results were not statistically different from the control values, the amounts cited may represent therapy administered for no OS benefit at all. So that the estimate here represents a best case estimate.

\(^g\)QALYs = Quality-adjusted life years. A measure of the impact of a treatment intervention. If an action gives a person an extra year of healthy life, that counts as one QALY. For these calculations a best case outcome has assumed any extension of OS is of good quality, although very often in oncology this is not the case.
example, by the numerous quality of life (QOL) instruments evaluated as part of the E2100 study (24). Despite endorsement by professional and patient advocacy organizations, reliance on marginal differences in PFS risks overestimating benefit and underestimating potential harm. Such advocacy also overlooks the problem such expensive therapies bring to our health care system (36).

The Potential for Harm: The Example of Agents Targeting the Epidermal Growth Factor Receptor Pathway

The indiscriminate use of marginal therapies can be harmful because the majority of patients either accrue no benefit or potentially may be harmed. Patients harmed include those who derive no benefit but endure toxicities that affect the quality of their life and those in whom a drug or a drug combination is less effective, either through biological interference, or through toxicity-related dose reductions. A well-studied example that highlights how therapies that achieve marginal benefit in a population might actually harm a fraction of patients is the use of cetuximab in colorectal cancer, a therapy already discussed above. Cetuximab was approved under the FDA’s accelerated approval program, which allows FDA to approve products for cancer and other serious or life-threatening diseases on the basis of early evidence of a product’s effectiveness (37). Following the FDA approval, cetuximab use increased rapidly and a majority of the 50,000 patients diagnosed with colon cancer in the United States each year then began receiving cetuximab. However, it was subsequently discovered that as many as 40% of patient’s tumors harbored KRAS mutations and that these patients did not benefit and may have been harmed (Figs. 2 and 3; refs. 38, 39). At a minimum, their PFS was reduced and they experienced toxicities, often grades 3-4, without the possibility of any antitumor effect. If one estimates that 20,000 patients with tumors harboring mutant KRAS were treated each year, then nearly 100,000 patients received unhelpful and potentially detrimental therapy before it became apparent that harm might be the outcome of receiving cetuximab. But looking at the 60% of patients in whom KRAS is wild-type, one sees that the cetuximab benefit is still marginal, perhaps not unexpected, given the complexity of the EGFR pathway. It has, thus, not been surprising that mutations and/or alterations in downstream molecules, other than RAS, have now been implicated to similarly confer an adverse impact following cetuximab (40–45). Identification of KRAS mutational status began the process of withholding cetuximab from patients who will not have benefit. However, there remains a pressing need to further define which cancer patients may benefit from cetuximab if this agent is to make a major contribution of cancer therapy (Fig. 4).

The Challenge of Identifying Patient Subsets That May Potentially Be Helped and Those That May Be Harmed

The expectation of a marginal outcome in a clinical trial often leads to enrollment of a large number of patients to
ensure statistical validity and to planned analyses of subgroups, hoping to find a subgroup that might derive benefit. However, when these planned subgroup analyses identify a subgroup with a hazard ratio (HR) that is either insignificant or strongly trends in a "negative" direction, this potentially valuable clinical information is then often ignored. For example, the FLEX trial, which found a 1.2-month survival advantage for cetuximab in the general population, showed that cetuximab plus chemotherapy was associated with a lower risk of progression or death in patients whose tumors harbor a mutant KRAS. A meta-analysis of clinical trials shows the harm of adding cetuximab to chemotherapy in patients whose tumors harbor a mutant KRAS.

**Fig. 3.** A meta-analysis of clinical trials shows the harm of adding cetuximab to chemotherapy in patients whose tumors harbor a mutant KRAS.
population, discovered that the interaction between the treatment and the ethnic origin was significant, with benefit seen only in patients who were white ($P = 0.011$; ref. 12). Yet, the ASCO Clinical Practice Guideline for stage IV NSCLC recommended broadly that clinicians “consider the addition of cetuximab to cisplatin-vinorelbine in first-line therapy…” choosing to ignore ethnic origin (14).

Why should this be so? Why would ASCO issue a provisional oncology opinion (PCO) on “testing for KRAS mutations in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy” (39), yet not issue such an opinion for a “clinical parameter”? Why did lung cancer specialists realize that Asian women with adenocarcinoma NSCLC histology who had not smoked have a better response to gefitinib and erlotinib, yet only become convinced of their clinical observations when EGFR mutations were eventually identified (46–48)? Part of our reluctance to accept clinical parameters such as age, gender, ethnic origin, and even performance status, likely emanates from their perceived “softness.” Oncologists seem to place greater trust in a laboratory endpoint.

The Remedy: Toward Biological Identification of Patient Subgroups

Given the limitations of subgroup selection based on clinical criteria as discussed above, more objective and definitive selection criteria are required. The obvious choice involves biological characterization, particularly as targeted agents are introduced into practice.

But, the trust we place on a given test must be “earned”; that is, it must be carefully developed and validated, be conducted in concert with therapeutic trials, and meet the same kinds of levels of evidence we expect of new therapeutic agents (49). This process has not always been the case with “biomarkers.” It seems obvious that detection of EGFR might contribute to understanding the likelihood of benefit for an EGFR inhibitor such as cetuximab; however, this is clearly not the case. Looking again to the FLEX trial, the ASCO Guidelines recommend adding “cetuximab to cisplatin-vinorelbine in first-line therapy in patients with an EGFR-positive tumor as measured by immunohistochemistry” (14). Yet in the FLEX trial, 85% of tumors were positive because positive was defined as “immunohistochemical evidence of EGFR expression in at least one positively stained tumor cell.” A marker found in 85% of patients in the FLEX study and in 89% in a second cetuximab lung cancer trial is hardly a paragon of personalized medicine (12, 50). Similarly, other EGFR markers, including “FISH positivity,” did not correlate with cetuximab efficacy (51). Finally, very meager “evidence” suggests mutations in EGFR do not influence the response to cetuximab (52). One must wonder if EGFR is the target or are our assays of any value. Or is it possible that, given the meager activity of cetuximab in NSCLC, it is difficult to discern these relationships?

Conclusions: Targeted Therapies, Marginal Benefits, and the Need for More Accurate Biological Characterization of Patients

The rather limited benefits observed to date from the application of therapies targeting the EGFR and VEGFR pathways and the limited progress in defining clinical populations clearly benefiting have led some to question whether biologically targeted agents represent a positive step forward. Clearly, the nature of drug development must evolve, including improved trial designs, and with better delineation of patient groups that benefit, are not helped, and are potentially harmed (53). This evolution needs to be a priority for the biomedical research community so that medical oncologists can better serve and help their patients (54). Application of targeted agents to patients classified and entered into clinical trials on the basis of morphologic disease classifications is outdated, inefficient, and increases the size, cost, duration, and risk of registration clinical trials. If targeted agents are to be studied, registered, and ultimately made available for general clinical use, patient populations will have to be
redefined. We consider it unlikely that measurement of individual "biomarkers" will predict clinical response to a therapeutic. Biological characterization must describe areas of tumor biology relevant to therapeutic effectiveness: the underlying patient-specific abnormality and the integrity of cell death and survival pathways as examples, as well as drug transport mechanisms when relevant to potential therapeutic agents. Furthermore, such "companion diagnostics" or "theranostics" must be developed in parallel with the therapeutic agents, and must have test validity (well-characterized repeatability, reproducibility, and other measures of test accuracy), established clinical validity (robust levels of clinical evidence showing their role in clinical decision making), and clinical utility (socioeconomic justification for the therapeutic use with the aid of the diagnostic). The FDA, in recent public meetings and published statements, has indicated their intention to more closely regulate the whole area of laboratory developed tests (LDT), reflecting their perception of the increasing importance of biological characterization in the practice of medicine (55, 56).

We conclude that although development of agents against relevant cancer-associated targets is a necessary part of the path toward more complete treatment solutions for patients, having a relevant target and an agent that effectively addresses this target are not sufficient for the development of new therapeutics. Unfortunately, efforts linking biological characterization with therapeutic application and clinical outcome tend to be "academic," isolated, variably funded or underfunded, and underpowered, using non–good laboratory practice laboratory procedures with assays of unclear test validity. New biological technologies allow us great insight into the biology of tumors before, during, and after therapy; it is through combining use of these technologies with our drug development and clinical trials activity that we will develop truly more effective cancer therapy. We call on regulators, patient advocates, oncology professional associations, and payors to encourage, fund, cooperate, and ultimately appropriately reimburse new technologies to more accurately match patients with appropriate therapies. Only in this way will we stop making too much of too little and achieving too little by giving too much.

Disclosure of Potential Conflicts of Interest

D. Parkinson, employment, stockholder, Nodality, Inc.; stockholder, Threshold, Inc.

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