Targeted Therapies for Cancer 2004

Jeffrey S. Ross, MD,1,2 David P. Schenkein, MD,2 Robert Pietrusko, PharmD,2 Mark Rolfe, PhD,2 Gerald P. Linette, MD, PhD,2,3 James Stec,2 Nancy E. Stagliano, PhD,2 Geoffrey S. Ginsburg, MD, PhD,2 W. Fraser Symmans, MD,4 Lajos Pusztai, MD, PhD,4 and Gabriel N. Hortobagyi, MD4

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Abstract

The regulatory agency approvals in the United States and Europe of imatinib mesylate (Gleevec) for patients with bcr/abl-positive chronic myelogenous leukemia, cetuximab (Erbitux) for patients with epidermal growth factor receptor overexpressing metastatic colorectal cancer, the antiangiogenesis agent bevacizumab (Avastin), and the proteasome inhibitor bortezomib (Velcade)—and the considerable public interest in new anticancer drugs that take advantage of specific genetic defects that render the malignant cells more likely to respond to specific treatment—are driving a new era of integrated diagnostics and therapeutics. The recent discovery of a drug response predicting activating mutation in the epidermal growth factor receptor gene for patients with non–small cell lung cancer treated with gefitinib (Iressa) has intensified this interest. In this review, the history of targeted anticancer therapies is highlighted, with focus on the development of molecular diagnostics for hematologic malignancies and the emergence of trastuzumab (Herceptin), an antibody-based targeted therapy for HER-2/neu overexpressing metastatic breast cancer. The potential of pharmacogenomic strategies and the use of high-density genomic microarrays to classify and select therapy for cancer are briefly considered. This review also considers the widely held view that, in the next 5 to 10 years, the integration of molecular oncology and molecular diagnostics will further revolutionize oncology drug discovery and development; customize the selection, dosing, route of administration of previously approved traditional agents and new therapeutics in clinical trials; and truly personalize medical care for patients with cancer.

Targeted Therapies for Cancer: Definitions

During the last several years, multiple definitions for the term targeted therapy have emerged [Table I]. First, the US Food and Drug Administration (FDA) has considered targeted therapy as a drug with an approved label in which there is a specific reference to a simultaneously or previously approved diagnostic test that must be performed before the patient can be considered eligible to receive the drug. Examples of this definition for targeted therapy are the coapprovals of trastuzumab and the eligibility diagnostic tests for the
selection of patients featuring HER-2/neu protein overexpression or gene amplification (HercepTest, DAKO, Carpinteria, CA; Pathway, Ventana Medical Systems, Illkirch Cedex, France; and PathVysion, Vysis, Downers Grove, IL) and cetuximab and the eligibility test for EGFR overexpression (EGFR PharmDx, DakoCytomation, Glostrup, Denmark). In this setting, the FDA Office of Combination Products describes these anticancer agents as “virtual” combination products that, in concept and labeling, must be used together to achieve the intended use, indication, or effect but are not packaged together.8

Second, for many scientists and oncologists, targeted therapy is defined as a drug with a focused mechanism that specifically acts on a well-defined target or biologic pathway that, when inactivated, causes regression or destruction of the malignant process. Examples of this type of targeted therapy include hormonal-based therapies in breast and prostate cancer; small-molecule inhibitors of the EGFR pathway in lung, breast, and colorectal cancers; blockers of invasion and metastasis enabling proteins and enzymes; antiangiogenesis agents; proapoptotic drugs; and proteasome inhibitors.

Third, many investigators consider anticancer antibodies, especially when conjugated with cytotoxic radioisotopes, cytotoxic drugs, and cellular poisons that seek out and kill malignant cells bearing the target antigen, as an additional type of targeted therapy.

The Ideal Target

The ideal cancer target [Table 2] can be defined as a macromolecule that is crucial to the malignant phenotype and is not expressed significantly in vital organs and tissues; that has biologic relevance that can be measured reproducibly in readily obtained clinical samples; that is definably correlated with clinical outcome; and that when interrupted, interfered with, or inhibited, a clinical response is yielded in a significant proportion of patients whose tumors express the target when target interrupted, interfered with, or inhibited

Minimal responses in patients whose tumors do not express the target

Table 2

Features of the Ideal Anticancer Target

Crucial to the malignant phenotype
Not significantly expressed in vital organs and tissues
A biologically relevant molecular feature
Reproducibly measurable in readily obtained clinical samples
Correlated with clinical outcome
Clinical response in a significant proportion of patients whose tumors express the target when target interrupted, interfered with, or inhibited
Minimal responses in patients whose tumors do not express the target

Table 3

Types of Targeted Therapy for Cancer

Antibodies

The early promise of mouse monoclonal antibodies for the treatment of human cancers was not realized owing to a combination of factors that included unfocused target selection that led to the identification of target antigens not critical for cancer cell survival and progression; low overall potency of naked mouse antibodies as anticancer drugs; poor tumor cell penetration of antibodies; limited success in producing radioisotope and toxin conjugates; and the development of human antimouse antibodies (HAMAs), preventing the use of multiple dosing schedules.15 During the early 1980s, the use of recombinant DNA technology was applied to antibody design to reduce the antigenicity of murine and other rodent-derived monoclonal antibodies. Chimeric antibodies were developed in which the constant domains of the human IgG

bind to primary and metastatic cancer cells with high affinity and create antitumor effects by complement-mediated cytolysis and antibody-dependent, cell-mediated cytotoxicity (naked antibodies) or by the focused delivery of radiation or cellular toxins (conjugated antibodies).9-14 Currently, there are 8 anticancer therapeutic antibodies approved by the FDA for sale in the United States and 1 antibody therapeutic antibody approved in Europe only.
molecule were combined with the murine variable regions by transgenic fusion of the immunoglobulin genes; the chimeric monoclonal antibodies were produced from engineered hybridomas and CHO cells.16,17 The use of chimeric antibodies significantly reduced the HAMA responses but did not completely eliminate them.18,19 Although several chimeric antibodies significantly reduced the HAMA responses but did not completely eliminate them, the development of therapeutic antibodies for cancer.9-12,15,24-26 The conjugation of radioisotopes, small-molecule cytotoxic drugs, and protein toxins to the targeting antibodies followed by deimmunized antibodies with variable domains genetically linked to human IgG, and primatized antibodies that featured a chimeric antibody structure of human and monkey that reduced immunogenicity and enabled the capability for continuous repeated dosing and long-term therapy.21,22 Finally, fully human antibodies have been developed using murine sources and transgenic techniques.23

These modern antibody design and deimmunization technologies have significantly improved the efficacy and reduced the toxicity of anticancer antibody therapeutics.9,12,15,24-26 The conjugation of radioisotopes, small-molecule cytotoxic drugs, and protein toxins to the targeting antibodies and the enhancement of effector function of antibody-dependent cellular cytotoxicity have enhanced the efficacy of anticancer antibody drugs. Toxicity has been a major obstacle in the development of therapeutic antibodies for cancer.9-12 Cross-reactivity with normal tissues can cause significant side effects, including dyspnea from pulmonary toxic effects, occasional central and peripheral nervous system complications, decreased liver function, renal damage, and, on occasion, unexpected toxic effects such as the heart muscle damage associated with the use of trastuzumab. In addition, radioimmunotherapy with isotopic-conjugated antibodies also can cause bone marrow suppression.

As shown in Table 3, of the 9 anticancer antibodies on the worldwide market, 2 are conjugated with radioisotopes and 1 is conjugated to a complex natural product toxin. Conjugation procedures have been designed to improve the efficacy of antibody therapy and have used a variety of methods to complex the isotope, toxin, or cytotoxic agent to the antibody.9,10 Cytotoxic small-molecule drug conjugates have been tested widely, but enthusiasm for this approach has been limited by the relatively low potency of these compounds.9 Fungal-derived potent toxins have yielded greater success with the calicheamicin-conjugated anti-CD33 antibody, gemtuzumab ozogamicin, approved for the treatment of patients with acute myelogenous leukemia (AML) who are older than 60 years, and a variety of antibodies conjugated with the fungal toxin maytansinoid (DM-1) in preclinical development and early clinical trials. The interest in radioimmunotherapy increased significantly in 2001 with the FDA approvals of the yttrium 90 (90Y)-conjugated anti-CD20 antibody Y90-ibritumomab tiuxetan and the iodine 131 (131I)-conjugated anti-CD20 antibody I131-tositumomab.
Antibody Therapeutics for Hematologic Malignant Neoplasms

The earliest and most successful clinical use of antibodies in oncology has been for the treatment of hematologic malignant neoplasms.9-12,27-31

Rituximab (Rituxan)

Approved in 1997, rituximab is arguably the most commercially successful anticancer drug of any type since the introduction of taxanes. Rituximab sales exceeded $700 million in the United States in 2001.32 Targeting the CD20 surface receptor common to many B-cell non-Hodgkin lymphoma subtypes, rituximab is a chimeric monoclonal IgG1 antibody that induces apoptosis, antibody-dependent cell cytotoxicity, and complement-mediated cytotoxicity that has achieved significantly improved disease-free survival rates compared with the use of cytotoxic agents alone.33-36

Y90-Ibritumomab Tiuxetan (Zevalin)

Y90-ibritumomab tiuxetan consists of the murine version of the anti-CD20 chimeric monoclonal antibody, rituximab, that has been linked covalently to the metal chelator, MD-DTPA, permitting stable binding of 111In when used for radionucleotide tumor imaging and 90Y when used to produce enhanced targeted cytotoxicity.37-40 In early 2002, Y90-ibritumomab tiuxetan became the first radioconjugated antibody therapeutic for cancer approved by the FDA. Since its approval, numerous patients who have received Y90-ibritumomab tiuxetan after their disease became refractory to a rituximab-based regimen have achieved significant responses.38,39

Gemtuzumab Ozogamicin (Mylotarg)

The approval of gemtuzumab ozogamicin by the FDA in 2000 marked the first introduction of a plant toxin–conjugated antibody therapeutic.41-45 Gemtuzumab ozogamicin is targeted against CD33, a surface marker expressed by 90% of myeloid leukemic blasts but absent from stem cells, armed with calicheamicin, a potent cytotoxic antibiotic that inhibits DNA synthesis and induces apoptosis.41 The current indication for use of gemtuzumab ozogamicin is for patients with AML who are older than 60 years, with the recommendation that, before the initiation of therapy, the leukemic blast count be less than 30,000/mL.42-44

Alemtuzumab (Campath)

Alemtuzumab, a humanized monoclonal antibody, was approved in mid 2001 for the treatment of B-cell chronic lymphocytic leukemia in patients who have been treated with alkylating agents and in whom fludarabine therapy has failed.32,46

Daclizumab (Zenapax)

Daclizumab is a chimeric monoclonal antibody that targets the interleukin-2 receptor. This antibody is used primarily to prevent and treat organ transplant rejection, but it also has been used in a wide variety of chronic inflammatory conditions, including psoriasis, multiple sclerosis, ulcerative colitis, asthma, type 1 diabetes mellitus, and uveitis and also in a variety of leukemias.47,48

I131-Tositumomab (Bexxar)

I131-tositumomab is a radiolabeled anti-CD20 murine monoclonal antibody approved in 2003 for the treatment of relapsed and refractory follicular/low-grade and transformed non-Hodgkin lymphoma.49,50

Antibody Therapeutics for Solid Tumors

Interest in the development of antibody therapeutics for solid tumors among many commercial organizations and universities has been impacted significantly by the technology advances in antibody engineering and the approval and recent clinical and commercial success of trastuzumab.

Trastuzumab (Herceptin)

During the mid 1980s, the discovery of the HER-2/neu (c-erb-B2) gene and protein and subsequent association with an adverse outcome in breast cancer provided clinicians with a new biomarker that could be used to guide adjuvant chemotherapy.51 The development of trastuzumab (Herceptin), a humanized monoclonal antibody designed to treat advanced metastatic breast cancer in which first- and second-line chemotherapy had failed, caused rapid, wide adoption of HER-2/neu testing of the patients' primary tumors.52 Since its launch in 1998, trastuzumab has become an important therapeutic option for patients with HER-2/neu–positive breast cancer.53-56

Reports that fluorescence in situ hybridization (FISH) could outperform immunohistochemical analysis in predicting trastuzumab response23 and the well-documented lower response rates of tumors staining immunohistochemically as intermediate (2+) vs intense (3+)57 has resulted in a variety of approaches for patient testing.3 In addition, including immunohistochemical analysis as a primary screen with follow-up FISH testing of 1+ cases, 2+ cases, or both, or primary FISH-based testing. Trastuzumab has achieved notable results in the treatment of HER-2/neu–positive advanced metastatic disease and is under extensive evaluation in major clinical trials for its potential efficacy when used in earlier stages of breast cancer.

Cetuximab (Erbitux)

The epidermal growth factor receptor (EGFR; HER1) is the target of several small-molecule drugs and the
recently approved antibody cetuximab. Cetuximab, a chimeric monoclonal antibody, binds to the EGFR with high affinity, blocking growth-factor binding, receptor activation, and subsequent signal-transduction events leading to cell proliferation. Cetuximab enhanced the antitumor effects of chemotherapy and radiotherapy in preclinical models by inhibiting cell proliferation, angiogenesis, and metastasis and by promoting apoptosis. Cetuximab has been evaluated alone and in combination with radiotherapy and various cytotoxic chemotherapeutic agents in a series of phase 2 and phase 3 studies that primarily treated patients with head and neck or colorectal cancer. Breast cancer trials also are underway.

Although the FDA approval process for cetuximab initially was slowed owing to concerns about clinical trial design and outcome data management, the antibody was approved in February 2004 for use in combination with CPT-11 for the treatment of advanced and refractory metastatic colorectal cancer. Similar to trastuzumab, the development of cetuximab also included an immunohistochemical test for determining EGFR overexpression to define patient eligibility to receive the antibody.

Bevacizumab (Avastin)

Bevacizumab (rhuMAb-VEGF) is a humanized murine monoclonal antibody targeting the vascular endothelial growth factor (VEGF). VEGF regulates vascular proliferation and permeability and functions as a survival factor for newly formed blood vessels.

In clinical trials for advanced metastatic breast cancer, the initial results of the combination treatment of bevacizumab and paclitaxel showed antitumor activity, but the results of follow-up studies were not convincing that the targeting of VEGF in this clinical setting would be effective. Bevacizumab also has been combined with trastuzumab in a 2-antibody therapeutic strategy for HER-2/neu–overexpressing breast cancer.

The phase 2 study evaluating bevacizumab in metastatic renal cell carcinoma reached its prespecified efficacy endpoint earlier than expected. Although late-stage clinical trials using bevacizumab with 5-fluorouracil, leucovorin, and CPT-11 in third-line treatment for advanced colorectal cancer did not achieve all of the major endpoints, when bevacizumab was used in first-line combination with 5-fluorouracil, a 5.5 month improvement in overall survival was observed. These data led to the FDA approval of bevacizumab for the treatment of metastatic colorectal cancer in February 2004. Unlike cetuximab, the development of bevacizumab has not included a diagnostic eligibility test. To date, neither direct measurement of VEGF expression nor assessment of tumor microvessel density has been incorporated into the clinical trials or linked to the rates of response to this antibody.

Edrecolomab (Panorex)

Edrecolomab is a murine IgG2A monoclonal antibody that targets the human tumor-associated antigen epithelial cell adhesion molecule (17-1A). Edrecolomab has been
approved in Europe (Germany) since 1995, but has not been approved by the FDA. In a study of 189 patients with resected stage III colorectal cancer, treatment with edrecolomab resulted in a 32% increase in overall survival compared with no treatment \((P < .01)\).\textsuperscript{74} The antitumor effects of edrecolomab are mediated through antibody-dependent cellular cytotoxicity, complement-mediated cytolyis, and the induction of an anti-idiotypic network.\textsuperscript{75} Edrecolomab also is being tested in large multicenter adjuvant phase 3 studies in stage II and stage III rectal cancer, stage II colon cancer, and metastatic breast cancer.\textsuperscript{76} Results from a recent randomized clinical trial showed that the addition of edrecolomab provided no benefit if given to patients with resected stage III colorectal carcinoma receiving adjuvant 5-fluorouracil and leucovorin.\textsuperscript{77}

In addition to the approved antibody therapeutics described in the preceding sections, a variety of additional antibody-based approaches for the treatment of cancer are applying novel approaches in various stages of clinical trials.

\textbf{huJ591 (Anti-PSMA\textsubscript{EXT})}

This antibody-based targeted therapy is an example of a new approach toward the treatment of hormone-refractory metastatic prostate cancer. Prostate-specific membrane antigen (PSMA) is a membrane-bound glycoprotein restricted to normal prostatic epithelial cells, primary and metastatic prostate cancer, and the endothelium of the neovasculature of a wide variety of nonprostatic carcinomas and other solid tumors.\textsuperscript{78-80}

The PSMA expression per cell increases progressively from low-grade to high-grade primary prostate cancer, from localized to metastatic hormone-sensitive prostate cancer, and in hormone-refractory metastatic disease \textit{Image 2}.\textsuperscript{78-80} Increasing expression levels of PSMA in resected primary prostate cancer is associated with increased rates of subsequent disease recurrence.\textsuperscript{81} In addition, significant PSMA expression has been identified in the tumor vasculature of a variety of nonprostatic tumors, including colon, lung, breast, and kidney cancers.\textsuperscript{80}

A deimmunized antibody targeting the extracellular domain of PSMA (huJ591) conjugated with \(^{90}\text{Y}\) has shown promising results for the treatment of hormone-refractory metastatic prostate cancer.\textsuperscript{82,83} In addition, the same anti-PSMA (huJ591) antibody targeting the external domain of the PSMA protein conjugated with the fungal toxin maytansinoid (DM-1) has completed preclinical development and is in early-stage clinical trials for the treatment of hormone-refractory metastatic disease.\textsuperscript{84} Radioconjugated antibodies to PSMA also have been used as diagnostic imaging agents (Image 2), including the commercially available ProstaScint test (Cytogen Corp, Princeton, NJ).\textsuperscript{85,86}

\textbf{Selected Targeted Anticancer Therapies Using Small Molecules}

\textbf{Hormonal Therapy for Breast Cancer}

Arguably the first type of targeted therapy in oncology \textit{Table 4} was the development of antiestrogen
therapies for patients with breast cancer that expressed the estrogen receptor (ER) protein. Originally developed as a competitive dextran-coated charcoal (DCC) radioligand binding assay performed on fresh tumor protein extracts and used to select patients for ablative endocrine surgery, the ER and progesterone receptor (PR) test format converted to an immunohistochemical platform when the decreased size of primary tumors associated with mass screening programs yielded insufficient tumor tissue for the DCC assay.

ER and PR testing has guided the use of the drug tamoxifen (Nolvadex), the most widely prescribed antiestrogen for the treatment of metastatic breast cancer and for chemoprevention of the disease in high-risk women. Although ER and PR testing is the front line for predicting tamoxifen response, additional biomarkers have been used to further refine therapy selection. The introduction of specific estrogen response modulators and aromatase inhibitors such as anastrozole (Arimidex), letrozole (Femara), and the combination chemotherapeutic, exemestane (Emcyt) have added new strategies for evaluating tumors for hormonal therapy.

### All-Trans Retinoic Acid (ATRA)

ATRA was developed specifically for the treatment of acute promyelocytic leukemia (Table 4) that features a disease-defining, retinoic acid receptor–activating t(15:17) reciprocal translocation. For these selected patients, direct targeting of the retinoic acid receptor with ATRA has resulted in high overall disease response rates, delay in disease progression, and long-term cures for many.

### Imatinib Mesylate (Gleevec)

The fast-track FDA approval of imatinib for patients with bcr/abl translocation defining CML in 2001 was accompanied by an excitement in the scientific and public communities for the future potential of low-toxicity, targeted anticancer therapy. Treatment with imatinib, an adenosine triphosphate–binding selective inhibitor of bcr-abl, has been associated with durable complete hematologic and complete cytogenetic remissions with minimal toxic effects in the early chronic phase of CML.

Imatinib has received regulatory approval for the treatment of relapsed and metastatic gastrointestinal stromal tumors (GISTs), which characteristically feature an activating

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**Table 4**

Selected Small-Molecule Drugs Designed to Target Specific Genetic Signatures and Biologic Pathways Critical to Cancer Growth and Progression

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Source</th>
<th>Clinical Development Status</th>
<th>Comment</th>
<th>Requires Eligibility Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>PML/RAR-α in PML</td>
<td>ATRA</td>
<td>Promega, Madison, WI</td>
<td>Approved</td>
<td>First true targeted therapy since the introduction of ER testing and hormonal therapy for breast cancer</td>
<td>Yes</td>
</tr>
<tr>
<td>bcr/abl in CML</td>
<td>Imatinib</td>
<td>Novartis, Basel, Switzerland</td>
<td>Approved</td>
<td>Has emerged as standard of care for early stage CML</td>
<td>Yes</td>
</tr>
<tr>
<td>c-kit in GIST; PDGF-α</td>
<td>Imatinib</td>
<td>Novartis</td>
<td>Approved</td>
<td>Responses in relapsed and metastatic GIST can be predicted by the location of the activating c-kit mutation</td>
<td>Yes</td>
</tr>
<tr>
<td>flt-3 in AML</td>
<td>SU5416; PKC412; MLN-518</td>
<td>Pfizer, New York, NY; Novartis; Millennium, Cambridge, MA</td>
<td>Early-stage clinical trials</td>
<td>Small-molecule drugs that target the flt-3 internal tandem duplication seen in 30% of AML cases</td>
<td>Yes</td>
</tr>
<tr>
<td>EGFR in NSCLC</td>
<td>Gefitinib</td>
<td>Astra Zeneca, Manchester, England</td>
<td>Approved</td>
<td>Preclinical activity in breast cancer; clinical trials ongoing</td>
<td>No</td>
</tr>
<tr>
<td>EGFR in glioblastoma</td>
<td>Erlotinib</td>
<td>Genentech, South San Francisco, CA; OSI, Melville, NY</td>
<td>Pending</td>
<td>In late-stage trials in NSCLC and recently (ASCO 2003) has shown efficacy in treatment of high-grade malignant gliomas</td>
<td>In development</td>
</tr>
<tr>
<td>Antiangiogenesis</td>
<td>Thalidomide; SU5416; ZD6474; endostatin; marimastat; others</td>
<td>Celgene, San Diego, CA; Pfizer/Sugen, South San Francisco, CA; Astra Zeneca; Entremed, Rockville, MD; British Biotech, Oxford, England; others</td>
<td>Pending</td>
<td>Thalidomide approved for treatment of leprosy and widely used to treat multiple myeloma; other agents in early- and mid-stage clinical trials</td>
<td>No</td>
</tr>
<tr>
<td>bcl-2</td>
<td>G3139; (oblimersen sodium [Genasense])</td>
<td>Genta, Berkeley, CA</td>
<td>Pending</td>
<td>Antisense oligonucleotide targets the anti-apoptotic gene, bcl-2</td>
<td>No</td>
</tr>
<tr>
<td>Proteasome in multiple myeloma</td>
<td>Bortezomib</td>
<td>Millennium</td>
<td>Approved</td>
<td>Proteasome inhibition effective in hematologic malignant neoplasms, but of uncertain potential for treatment of solid tumors</td>
<td>No</td>
</tr>
</tbody>
</table>

AML, acute myelogenous leukemia; ASCO, American Society of Clinical Oncology; ATRA, all-trans retinoic acid; CML, chronic myelogenous leukemia; EGFR, epidermal growth factor receptor; ER, estrogen receptor; GIST, gastrointestinal stromal tumor; NSCLC, non–small cell lung cancer; PDGF, platelet-derived growth factor; PML, acute promyelocytic leukemia; RAR, retinoic acid receptor.
mutation in the c-kit receptor tyrosine kinase (RTK) gene.81 For GISTs, the response to imatinib treatment seems to be predictable based on the location of the c-kit mutation.102 The immunohistochemically based detection of c-kit overexpression in GISTs does not guarantee a response to imatinib in patients with metastatic disease because most commercially available antibodies for c-kit recognize the total c-kit and do not distinguish the activated or phosphorylated version, which is the actual target of imatinib. Although c-kit activation has not been linked to more common tumors such as breast cancer, the platelet-derived growth factor α, another target of imatinib, has been associated with the biology of these cancers.103

flt-3 Targeted Therapy

In approximately 30% of cases of AML and less frequently in other forms of leukemia, the activation of the flt-3 RTK (Table 4) by an internal tandem duplication or point mutation has been associated with a more aggressive form of the disease.104-106 Three novel small-molecule compounds for the treatment of AML that target flt-3 in clinical trials for the treatment of AML are all planning future tests for flt-3 status to determine patient eligibility.

Gefitinib (Iressa)

Gefitinib was approved by the FDA in 2003 as monotherapy for the treatment of patients with locally advanced or metastatic non–small cell lung cancer after failure of both platinum and docetaxel-based chemotherapies.107,108 Gefitinib is a small-molecule drug that targets EGFR. The approval of gefitinib did not include an eligibility diagnostic test for EGFR status designed to select patients whose tumors were more likely to respond to the drug. However, a recent study has identified an activating mutation in the tyrosine kinase portion of the EGFR gene in non–small cell lung cancer that appears to be predictive of the response to gefitinib.109 Overexpression of EGFR, typically identified by immunohistochemical analysis, is extremely common in lung and breast cancers,107-109 but, in contrast with HER-2/neu overexpression that is virtually limited to cases with gene amplification, multiple mechanisms of dysregulation of EGFR and associated activation of signaling pathways have been described in these tumors.107-109

Erlotinib (Tarceva)

Erlotinib is another targeted small-molecule inhibitor of EGFR in late-stage clinical trials for the treatment of non–small cell lung cancer, pancreatic cancer, and primary glioma.110-115 Erlotinib has shown efficacy in preclinical models of brain tumors112 and has shown promising results in the treatment of high-grade malignant gliomas. The clinical trials for erlotinib have included studies of the EGFR gene and protein status, but it is not known whether an eligibility diagnostic test will be required by the approval process for patients to receive the drug.

Antiangiogenesis Drugs (SU5416, Thalidomide, Endostatin, and Angiostatin)

In addition to bevacizumab, a variety of small-molecule drugs that target the establishment and growth of tumor blood vessels are in clinical trials for a variety of malignant neoplasms.116-119 To date, none of these compounds have been linked to a diagnostic test such as tumor microvessel density or the expression of an angiogenesis-promoting gene or protein in the clinical development plans.

G3139 (Oblimersen Sodium [Genasense])

Another emerging strategy in anticancer therapy is the targeting of chemotherapy resistance by overcoming the antiapoptosis mechanisms of cancer cells. An example of this approach is the novel antisense oligonucleotide G3139 that targets the antiapoptotic gene bcl-2.120-124 This agent has shown promise for the treatment of hematologic malignant neoplasms and malignant melanoma.

Bortezomib (Velcade)

Recently, drugs targeting the proteasome have been developed that are designed to impact downstream...
pathways regulating angiogenesis, tumor growth, cell adhesion, and resistance to apoptosis. One of these agents, bortezomib, was approved in May 2004 for the treatment of relapsed and refractory multiple myeloma. Bortezomib is under investigation for the treatment of early-stage multiple myeloma, non-Hodgkin lymphoma, and a variety of solid tumors, including lung cancer.

Pharmacogenomics and Personalized Medicine

Targeted therapy in oncology has been a major stimulus for the evolving field of pharmacogenomics. In its broadest definition, pharmacogenomics can encompass germline and somatic (disease) gene and protein measurements used to predict the likelihood that a patient’s tumor will respond to a specific single-agent or multigagent chemotherapy regimen and the risk of toxic side effects. During the next several years, the field of oncology drug development will see numerous products pass through the approval process and enter the market accompanied by diagnostic tests designed to “personalize” their use, dosage, route of administration, and length of treatment for each patient, one at a time. Only time will tell whether this new approach to anticancer pharmaceuticals will yield breakthrough results, reducing morbidity and mortality and improving outcomes for all who will be afflicted with the disease.

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