Cancer cells may acquire the capacity for autonomous and dysregulated proliferation through the uncontrolled production of specific molecules that promote cell growth (growth factors) or through abnormal, enhanced expression of specific proteins (growth factor receptors) on the cell membranes to which growth factors selectively bind. Both processes trigger a series of intracellular signals that ultimately lead to the proliferation of cancer cells, induction of angiogenesis, and metastasis. The majority of human epithelial cancers are marked by functional activation of growth factors and receptors of the epidermal growth factor receptor (EGFR) family. Given this phenomenon, EGFR was the first growth factor receptor to be proposed as a target for cancer therapy. After 20 years of drug development, four EGFR antagonists are currently available for the treatment of four metastatic epithelial cancers: non–small-cell lung cancer, squamous-cell carcinoma of the head and neck, colorectal cancer, and pancreatic cancer. Less information is available about the use of EGFR antagonists in the treatment of earlier stages of cancer. This article summarizes the mechanisms of action of EGFR inhibitors, presents the clinical evidence of their anticancer activity, and considers the current, and controversial, clinical issues with respect to their optimal use in the treatment of patients with cancer.

**EGFR in Human Carcinogenesis**

EGFR is a transmembrane receptor belonging to a family of four related proteins (Fig. 1). Ten different ligands can selectively bind to each receptor. After a ligand binds to a single-chain EGFR, the receptor forms a dimer that signals within the cell by activating receptor autophosphorylation through tyrosine kinase activity. Autophosphorylation triggers a series of intracellular pathways that may result in cancer-cell proliferation, blocking apoptosis, activating invasion and metastasis, and stimulating tumor-induced neovascularization.

**Development of EGFR Antagonists for Anticancer Therapy**

The first anti-EGFR drugs were developed in the 1980s. Two classes of EGFR antagonists have been successfully tested in phase 3 trials and are now in clinical use: anti-EGFR monoclonal antibodies and small-molecule EGFR tyrosine kinase inhibitors (Tables 1 and 2).

Anti-EGFR monoclonal antibodies, such as cetuximab, bind to the extracellular domain of EGFR when it is in the inactive configuration, compete for receptor binding by occluding the ligand-binding region, and thereby block ligand-induced EGFR tyrosine kinase activation. Small-molecule EGFR tyrosine kinase inhibitors, such as erlotinib and gefitinib, compete reversibly with ATP to bind to the intracellular catalytic domain of EGFR tyrosine kinase and, thus, inhibit EGFR autophosphorylation and downstream signaling. Anti-EGFR monoclonal antibodies recognize EGFR
exclusively and are therefore highly selective for this receptor. In addition, various small-molecule EGFR tyrosine kinase inhibitors can block different growth factor receptor tyrosine kinases, including other members of the EGFR family, or the vascular endothelial growth factor receptor. Various irreversible EGFR tyrosine kinase inhibitors are now in early stages of clinical development.\(^5,12\) The mechanism (or mechanisms) of action, pharmacologic effects, and spectrum of activity of anti-EGFR monoclonal antibodies and small-molecule EGFR tyrosine kinase inhibitors have differences that may be relevant for clinical activity (Table 1 and Fig. 2 and 3).\(^13\)

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**Figure 1. Signal Transduction Pathways Controlled by the Activation of EGFR.**

Three steps can be schematically defined in the activation of EGFR-dependent intracellular signaling.\(^2-17\) First, the binding of a receptor-specific ligand occurs in the extracellular portion of the EGFR or of one of the EGFR-related receptors (HER2, HER3, or HER4). Second, the formation of a functionally active EGFR-EGFR dimer (homodimer) or of an EGFR-HER2, EGFR-HER3, or EGFR-HER4 dimer (heterodimer) causes the ATP-dependent phosphorylation of specific tyrosine residues in the EGFR intracellular domain. Third, this phosphorylation triggers a complex program of intracellular signals to the cytoplasm and then to the nucleus. The two major intracellular pathways activated by EGFR are the RAS–RAF–MEK–MAPK pathway, which controls gene transcription, cell-cycle progression from the G1 phase to the S phase, and cell proliferation, and the PI3K–Akt pathway, which activates a cascade of anti-apoptotic and pro-survival signals. bFGF denotes basic fibroblast growth factor, HB-EGF heparin-binding EGF, MAPK mitogen-activated protein kinase, P phosphate, PI3K phosphatidylinositol 3,4,5-kinase, TGF\(\alpha\) transforming growth factor \(\alpha\), and VEGF vascular endothelial growth factor. For more detailed information, see Figure 1 in the Supplementary Appendix (available with the full text of this article at www.nejm.org).
Clinical Efficacy of EGFR Antagonists in Human Cancers

More than 10 EGFR-targeting agents are in advanced clinical development for the treatment of various human cancer types.\(^5,10,11,12\) Two anti-EGFR monoclonal antibodies (cetuximab and panitumumab) and two small-molecule, reversible EGFR tyrosine kinase inhibitors (gefitinib and erlotinib) have been approved in several countries for the treatment of metastatic non–small-cell lung cancer, colorectal cancer, squamous-cell carcinoma of the head and neck, and pancreatic cancer (Table 2).\(^20-24\) (For relevant clinical studies supporting the use of anti-EGFR drugs in the first three conditions, see Tables 1, 2, and 3 in the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

Non–Small-Cell Lung Cancer

Phase 1 trials showed that gefitinib and erlotinib have important clinical activity in patients with...
metastatic, chemoresistant non–small-cell lung cancer.25-29 Dose-dependent and reversible diarrhea and acneiform rashes have been the most prominent side effects (maximum tolerated dose, 750 mg per day for gefitinib and 150 mg per day for erlotinib). The histologic characteristics of the rash (a neutrophilic infiltrate in perifollicular areas within the basal layer of the skin) differ from those seen in typical acne and are common to all EGFR-targeted drugs, including anti-EGFR monoclonal antibodies.30 Skin toxicity is generally observed within 2 to 3 weeks after the start of treatment and gradually resolves in most patients, even when anti-EGFR treatment is continued. The maximum tolerated dose of erlotinib (150 mg per day), based on side effects, was chosen for further study, whereas for gefitinib, relatively low doses (patients were randomly assigned to receive 250 mg or 500 mg per day), given the maximum tolerated doses, were chosen.

Gefitinib was the first anti-EGFR agent that was shown, in two randomized phase 2 studies, to have clinically important antitumor activity in patients with non–small-cell lung cancer who had not had a response to one or more chemotherapy regimens, including platinum-based and docetaxel-based therapies.30-32 The two doses of gefitinib (250 mg and 500 mg) had similar antitumor activity, but toxicity was greater at the higher dose. Therefore, the lower dose was selected for further clinical studies. These trials led the Food and Drug Administration (FDA) in May 2003 to approve gefitinib as third-line therapy for patients with locally advanced or metastatic non–small-cell lung cancer after failure of both platinum-based and docetaxel-based chemotherapies.

However, a placebo-controlled, randomized phase 3 trial (the Iressa Survival Evaluation in Lung Cancer [ISEL] trial) failed to show that gefitinib was effective in improving survival.33 Neither median survival nor the rate of survival at 1 year differed significantly between patients receiving gefitinib and those receiving placebo in either the overall study population or a subgroup with a history of adenocarcinoma. Pre-

| Table 2. EGFR Inhibitors Currently Approved for Cancer Treatment.27 |
|-------------------|-----------------|-----------------|
| **Drug**          | **Molecular Properties** | **Approved Uses** |
| Erlotinib         | Reversible EGFR tyrosine kinase inhibitor (quinazoline-derivative molecule) | Erlotinib has been approved by several regulatory agencies worldwide, including the FDA and the EMEA in the European Union, as monotherapy for the treatment of non–small-cell lung cancer that is refractory to platinum-based chemotherapy. More recently, erlotinib has been approved by the FDA and the EMEA for use in combination with gemcitabine as first-line treatment for advanced pancreatic cancer. |
| Gefitinib         | Reversible EGFR tyrosine kinase inhibitor (quinazoline-derivative molecule) | Gefitinib has been approved in various countries for use as third-line treatment of non–small-cell lung cancer that is refractory to platinum-based and docetaxel-based chemotherapy regimens. After an accelerated approval process, it was approved by the FDA in May 2003 but has been withheld from the U.S. market since June 2005, as a result of the release of preliminary results of the ISEL trial, which assessed its use in patients with non–small-cell lung cancer that was refractory to previous platinum-based chemotherapy. Gefitinib has never been approved in the European Union but is currently on the market in Japan, Korea, China, and several other Asian countries. It is currently an investigational drug in the United States and the European Union. |
| Cetuximab         | Human–mouse chimeric monoclonal antibody (lgG1 subtype) | Cetuximab has been approved by several regulatory agencies worldwide, including the FDA and the EMEA, for the treatment of advanced colorectal cancer that is refractory to irinotecan-based chemotherapy (alone or in combination with irinotecan in the United States but only in combination with irinotecan in the European Union). Cetuximab in combination with radiotherapy is also approved for the treatment of locally advanced squamous-cell carcinoma of the head and neck. |
| Panitumumab       | Fully human monoclonal antibody (lgG2k subtype) | Panitumumab has been approved by several regulatory agencies worldwide, including the FDA, as monotherapy for third-line treatment of colorectal cancer that is refractory to fluoropyrimidines, oxaliplatin, or irinotecan. In December 2007, panitumumab was approved by the EMEA for use in patients with colorectal cancer who carry a normal, wild-type K-RAS gene. |

* EGFR denotes epidermal growth factor receptor, EMEA European Medicines Evaluation Agency, FDA Food and Drug Administration, and ISEL Iressa Survival Evaluation in Lung Cancer.
planned subgroup analysis showed a significant survival benefit only in patients of Asian origin and in those who had never smoked. In June 2005, on the basis of the lack of a survival benefit in the ISEL study, the FDA restricted the use of gefitinib to patients participating in a clinical trial or continuing to benefit from treatment already initiated. Currently, gefitinib is marketed in several countries in eastern Asia but is not available in the United States or the European Union.

More recently, two randomized phase 3 trials evaluated the effectiveness of gefitinib monotherapy as compared with that of standard chemotherapy (docetaxel) as second-line treatment for chemotherapy-refractory non–small-cell lung cancer. The V-15-32 trial, conducted in Japan, failed to demonstrate the noninferiority of gefitinib in terms of overall survival, which was the primary end point. However, in a large multicenter trial, this end point was achieved with gefitinib after platinum-based therapy had failed. In addition, the side-effect profile appeared to favor gefitinib.

In a phase 2 study, the antitumor activity of erlotinib as a single agent in heavily pretreated non–small-cell lung cancer was similar to that of gefitinib. More important, in the BR.21 trial, a phase 3, randomized, double-blind, placebo-controlled study involving patients with pretreated non–small-cell lung cancer, erlotinib increased median survival by approximately 2 months as compared with placebo (Table 3). Responses were significantly more frequent in women, in patients with adenocarcinoma, and in patients with no history of smoking. However, a significant survival advantage was observed in all patient subgroups after treatment with erlotinib as compared with placebo. Quality-of-life analysis supported the palliative benefit of erlotinib in extending the time during which patients were free of symptoms (cough, dyspnea, and pain). On the basis of these results, erlotinib was approved by the FDA in November 2004 and by the European Medicines Evaluation Agency (EMEA) in October 2005 for second- and third-line treatment of chemotherapy-resistant, advanced non–small-cell lung cancer. Several hypotheses have been proposed as to why the efficacy seems different for gefitinib and erlotinib in the similar BR.21 and ISEL phase 3 studies. One possible explanation is dosing: erlotinib was used at the maximum tolerated dose, whereas gefitinib was provided at a much lower dose.

On the basis of preclinical data demonstrating that anti-EGFR drugs potentiate the antitumor activity of cytotoxic drugs, four phase 3, double-blind, placebo-controlled, randomized clinical trials examined the combination of erlotinib or gefitinib with chemotherapy as first-line treatment for non–small-cell lung cancer. Two standard platinum-based, dual-drug regimens were used in combination with erlotinib or gefitinib. Neither a survival advantage nor a benefit with respect to the response rate or time to progression was seen with the addition of gefitinib or erlotinib to chemotherapy in any of these trials. One possible reason that these trials failed to demonstrate any advantage of gefitinib or erlotinib is that they were conducted in
unselected patients with non–small-cell lung cancer.\textsuperscript{44} Since only a subgroup of EGFR-positive patients with non–small-cell lung cancer have tumors that are dependent on the EGFR pathway, few patients with this type of cancer would have a clinical benefit from the addition of an anti-EGFR drug to chemotherapy.\textsuperscript{44} In addition, a retrospective subgroup analysis suggested that the addition of erlotinib to carboplatin and paclitaxel significantly prolonged survival only in the subgroup of patients who had never smoked.\textsuperscript{42}

Cetuximab treatment is said to have relatively few side effects. The most common adverse events include skin toxicity (flushing, an acnelike rash, and folliculitis), fever and chills, asthenia, transient elevations in aminotransferase levels, and nausea.\textsuperscript{45} Approximately 1.5% of patients have infusion reactions, which include allergic reactions requiring discontinuation of therapy; this rate is in keeping with the use of a chimeric human–mouse monoclonal antibody. Whereas cetuximab is marginally active as a single agent in advanced non–small-cell lung cancer, most phase 2 studies suggest that adding cetuximab to platinum-based therapies is of clinical benefit.\textsuperscript{46–50} A large, multicenter, randomized, phase 3 study in which cetuximab was added to standard platinum-based chemotherapy (cisplatin and vinorelbine) has recently been completed (ClinicalTrials.gov number, NCT00148798). A more thorough evaluation of the role of cetuximab in the treatment of advanced non–small-cell lung cancer awaits publication of the results of this trial.

**COLORECTAL CANCER**

Cetuximab has been evaluated in both chemotherapy-refractory and untreated metastatic colorect-
The overall response rate included complete and partial responses. * Patients with metastatic, platinum-refractory, non–small-cell lung cancer were treated either with erlotinib alone (150 mg per day) or with placebo until disease progression. Approximately half of the patients had also received a second-line treatment before study entry. Data are from Shepherd et al.37 CI denotes confidence interval. † The overall response rate included complete and partial responses.

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**Table 3. Efficacy of Erlotinib in Chemotherapy-Refractory Non–Small-Cell Lung Cancer.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N = 243)</th>
<th>Erlotinib (N = 488)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (%)†</td>
<td>&lt;1</td>
<td>9</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median progression-free survival (mo)</td>
<td>1.8</td>
<td>2.2</td>
<td>0.61 (0.51–0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median overall survival (mo)</td>
<td>4.7</td>
<td>6.7</td>
<td>0.70 (0.58–0.85)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

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In phase 2 studies, cetuximab monotherapy was associated with response rates of 9 to 12%. Response rates of approximately 20% were achieved when cetuximab was used in combination with irinotecan in patients who had not had a response to previous therapy with irinotecan.51–53 A multicenter, randomized, phase 2 trial evaluated the activity of cetuximab given alone or with irinotecan in patients who had not had a response to irinotecan monotherapy (Table 4).54 The cetuximab–irinotecan combination was significantly more effective than cetuximab monotherapy in terms of the response rate and rate of progression-free survival. However, the median survival was similar with the two approaches, mainly because of the crossover of patients from cetuximab monotherapy to the combination group on treatment failure. On the basis of these results, cetuximab was approved by the FDA in February 2004 for use in patients with metastatic colorectal cancer, either in combination with irinotecan (for patients who do not have a response to irinotecan alone) or as monotherapy (in patients who cannot tolerate irinotecan). The EMEA has approved cetuximab only in combination with irinotecan.

A multicenter, randomized, phase 3 trial examined the combination of cetuximab plus irinotecan as second-line treatment for colorectal cancer in patients who had not had a response to an oxaliplatin-based regimen. Cetuximab plus irinotecan was significantly better than irinotecan alone in improving response rates, increasing progression-free survival, and improving the quality of life.55 However, no differences were seen in overall survival, probably because almost half the patients crossed over to cetuximab treatment after the failure of irinotecan monotherapy. Recently, a randomized phase 3 trial comparing the use of cetuximab with best supportive care for patients in whom all available drugs, including fluoropyrimidines, oxaliplatin, and irinotecan, had failed showed that cetuximab increased progression-free survival, overall survival, and quality of life (Table 4).56 Cetuximab appears to be the only drug that does so with colorectal cancer who have had unsuccessful courses of all currently available chemotherapies.

Phase 2 studies57,58 indicate that cetuximab combined with both irinotecan and oxaliplatin-based chemotherapies may have a role in the first-line treatment of metastatic colorectal cancer, with a 10 to 20% absolute increase in response rates reported. Such a response could be clinically relevant, particularly for the management of metastatic disease limited to the liver, since reductions in the number and size of metastases after administration of the drug might present the opportunity for potentially curative surgery. Recently, a multicenter, randomized, phase 3 study evaluated the combination of cetuximab with a standard chemotherapeutic regimen of fluorouracil, leucovorin, and irinotecan (FOLFIRI) in previously untreated metastatic colorectal cancer. Cetuximab plus FOLFIRI significantly increased response rates, prolonged progression-free survival, and increased the number of patients who could undergo potentially curative surgical removal of liver metastasis by a factor of approximately three.59

Another monoclonal agent is panitumumab, a fully human anti-EGFR monoclonal antibody.22 As seen with cetuximab, skin toxicity and diarrhea are the most common side effects of this agent. A randomized phase 3 clinical trial compared the use of panitumumab with the best supportive care in patients with colorectal cancer who had previously been treated unsuccessfully with a fluoropyrimidine, oxaliplatin, and irinotecan. A 10% response rate was reported,
The combination of cetuximab and radiotherapy was initially tested in patients with previously untreated, locally advanced squamous-cell carcinoma of the head and neck. In a randomized, phase 3 clinical trial, patients were treated with radiotherapy alone or in combination with cetuximab. The addition of cetuximab to radiation therapy significantly prolonged progression-free survival, duration of locoregional control, and overall survival. A randomized phase 3 trial showed that the addition of cetuximab to platinum- and fluorouracil-based chemotherapy in the first-line treatment of recurrent or metastatic squamous-cell carcinoma of the head and neck showed a significantly higher response rate in the group that received cetuximab in combination with cisplatin (Table 5). This phase 3 study is unique in showing a survival benefit for a novel treatment in patients with platinum-resistant squamous-cell carcinoma of the head and neck. In a randomized, phase 3, controlled trial of cisplatin plus cetuximab as compared with placebo in patients with previously untreated, locally advanced squamous-cell carcinoma of the head and neck, a randomized phase 3 clinical trial, patients were treated with cetuximab alone (intravenous loading dose of 400 mg per square meter, followed by weekly intravenous doses of 250 mg per square meter) or with cetuximab (loading dose of 400 mg per square meter followed by 250 mg per square meter weekly) plus irinotecan until disease progression. Approximately two thirds of the patients had also received a line of treatment for metastatic disease with an oxaliplatin-based therapy before study entry. Data are from Cunningham et al.\textsuperscript{54}
mumab in the treatment group receiving the best supportive care. On the basis of these results, panitumumab was approved by the FDA in September 2006 as monotherapy for the treatment of metastatic colorectal cancer with disease progression after chemotherapy regimens consisting of a fluoropyrimidine, oxaliplatin, and irinotecan.

**Table 4. Efficacy of Cetuximab in Chemotherapy-Refractory Colorectal Cancer.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cetuximab (N = 111)†</th>
<th>Cetuximab plus Irinotecan (N = 218)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Best Supportive Care (N = 285)</th>
<th>Cetuximab (N = 287)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOND trial‡</td>
<td>Overall response rate (%)§</td>
<td>10.8</td>
<td>22.9</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to progression (mo)</td>
<td>1.5</td>
<td>4.1</td>
<td>0.54 (0.42–0.71)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median overall survival (mo)</td>
<td>6.9</td>
<td>8.6</td>
<td>0.91 (0.68–1.21)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCIC-CO.17 trial¶</td>
<td>Overall response rate (%)§</td>
<td>1.8</td>
<td>1.9</td>
<td>0.68 (0.57–0.80)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median progression-free survival (mo)</td>
<td>4.6</td>
<td>6.17</td>
<td>0.77 (0.64–0.92)</td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median overall survival (mo)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* CI denotes confidence interval, and NS not significant.
† Crossover to cetuximab plus irinotecan was allowed after progression in 56 patients (50%) treated initially with cetuximab alone.
‡ The Bowel Oncology with Cetuximab Antibody (BOND) trial was a randomized phase 2 trial. Patients with metastatic, irinotecan-refractory colorectal cancer were treated either with cetuximab alone (intravenous loading dose of 400 mg per square meter of body-surface area, followed by weekly intravenous doses of 250 mg per square meter) or with cetuximab (loading dose of 400 mg per square meter followed by 250 mg per square meter weekly) plus irinotecan until disease progression. Approximately two thirds of the patients had also received a line of treatment for metastatic disease with an oxaliplatin-based therapy before study entry. Data are from Cunningham et al.\textsuperscript{54}
§ The overall response rate included complete and partial responses.
¶ The NCIC-CO.17 trial was a randomized phase 3 trial. Patients with metastatic colorectal cancer that was refractory to fluorouracil, irinotecan, and oxaliplatin were treated either with cetuximab alone (intravenous loading dose of 400 mg per square meter, followed by weekly intravenous doses of 250 mg per square meter) or with best supportive care until disease progression. Crossover to cetuximab was not allowed after progression in the group that received best supportive care. Data are from Jonker et al.\textsuperscript{55}
Carcinoma of the head and neck. It was also approved as monotherapy for metastatic disease in patients who have not had a response to chemotherapy. In March 2006, the EMEA approved cetuximab in combination with radiotherapy for the treatment of locally advanced disease.

### Pancreatic Cancer

A single-group phase 2 study suggested that cetuximab was promising when used in combination with gemcitabine for the treatment of advanced pancreatic cancer. However, a more recent randomized phase 3 study failed to show a significant survival advantage with this combination as compared with standard treatment (gemcitabine monotherapy). In contrast, another randomized phase 3 trial, which compared the combination of erlotinib (100 mg per day) and gemcitabine with gemcitabine alone, showed a significant improvement in response and survival rates (hazard ratio for death, 0.82; 95% confidence interval, 0.69 to 0.99; \( P = 0.04 \); 1-year survival rate, 23% vs. 17%, \( P = 0.02 \), and both the FDA and EMEA have approved this regimen for first-line treatment of pancreatic cancer. Although the increase in survival could be considered modest in absolute terms, it showed that there is a significant advantage in adding an anticancer drug to gemcitabine in the treatment of metastatic pancreatic cancer — a unique finding.

### Predicting the Response to Anti-EGFR Drugs

Since only a subgroup of patients with cancer have a clinical benefit from treatment with EGFR inhibitors, there is an urgent need for identification and clinical validation of useful criteria for selecting patients for such treatment. A series of studies suggests that considering certain clinicopathological characteristics, as well as specific gene alterations, might help to identify patients whose cancers could be either sensitive or resistant to anti-EGFR therapy.

### Clinical and Pathological Predictors

Most clinical studies of gefitinib or erlotinib in non–small-cell lung cancer suggest that Asian
ethnic background, female sex, the absence of a history of smoking, and a tumor with histologic features of adenocarcinoma are potential predictors of a positive clinical response to anti-EGFR therapy. However, the presence or absence of cutaneous toxic effects, such as an acnelike rash, and their severity are the most important clinical correlates of the efficacy of anti-EGFR therapy. In fact, a significant positive correlation between cutaneous toxicity and rates of response, progression-free survival, and overall survival has been noted in virtually all trials of erlotinib, cetuximab, or panitumumab in advanced non–small-cell lung cancer, colorectal cancer, squamous-cell carcinoma of the head and neck, and pancreatic cancer. It is conceivable that the effects in skin not influenced by cancer reflect the extent of EGFR blockade achieved in the tumor, in which case the rash would correlate with EGFR saturation or with a relevant drug concentration within the tumor.

**EGFR PROTEIN EXPRESSION**

EGFR expression as determined by immunohistochemical methods was the first biomarker investigated as a potential predictor of response. However, most studies have failed to show any relationship between EGFR expression and the clinical activity of anti-EGFR drugs. Cetuximab has also been shown to have clinical activity in patients with colorectal cancer that is negative for EGFR. Similarly, in a prospective phase 2 clinical trial, the response to treatment with panitumumab in patients with metastatic colorectal cancer was similar whether EGFR protein expression was high, low, or negative, as assessed by immunohistochemical methods. Collectively, these data suggest that immunohistochemical testing for EGFR is not an optimal method for identifying patients who may have a response to treatment with anti-EGFR drugs.

**SOMATIC EGFR GENE MUTATIONS**

The discovery that certain somatic mutations within the tyrosine kinase, ATP-binding domain of the EGFR gene are associated with a response to EGFR tyrosine kinase inhibitors in non–small-cell lung cancer suggested that the selection of patients through molecular screening might be feasible. Approximately 90% of EGFR mutations affect small regions of the gene within exons (18 to 24) that code for the EGFR tyrosine kinase domain. The most common mutations are an in-frame deletion in exon 19 around codons 746 to 750 (accounting for 45 to 50% of EGFR mutations) and a missense mutation leading to a substitution of arginine for leucine at codon 858 (L858R) in exon 21 (35 to 45% of EGFR mutations). Somatic EGFR mutations are found in approximately 5 to 15% of unselected white patients and in 25 to 35% of unselected Asian patients with non–small-cell lung cancer. These mutations seem to be limited to non–small-cell lung cancer, since they have rarely been detected in other types of human cancer. Somatic mutations in the EGFR gene are most frequently detected in a subpopulation of patients with this form of cancer who have one or more of the following characteristics: histologic features of adenocarcinoma and, in particular, nonmuinous bronchioloalveolar carcinoma; an absence of a history of smoking; an absence of K-RAS gene mutations; Asian ethnicity; and female sex. The likelihood of EGFR mutations decreases as the exposure to tobacco smoke increases, leading to the hypothesis that lung adenocarcinoma in patients who have never smoked is a distinct form of non–small-cell lung cancer with a high frequency of EGFR mutations and increased sensitivity to EGFR tyrosine kinase inhibitors. The association between EGFR mutations and a response to erlotinib or gefitinib has been retrospectively confirmed in several clinical studies. It has been also suggested that this association translates into improved survival. However, in larger randomized studies, such as the BR.21 trial, a similar survival advantage was observed for patients treated with erlotinib, independently of the presence of EGFR mutations or of a wild-type EGFR gene, indicating that the presence of EGFR mutations is not the only biomarker for predicting a survival benefit of treatment with small-molecule EGFR tyrosine kinase inhibitors in patients with non–small-cell lung cancer.

**INCREASED EGFR COPY NUMBER**

The EGFR gene is rarely amplified in human cancers. However, fluorescence in situ hybridization (FISH) shows an increased EGFR copy number with balanced polysomy in a high proportion of cancer cells in approximately 25 to 40% of patients with non–small-cell lung cancer, squamous-cell carcinoma of the head and neck, or colorectal cancer. A single-group, phase 2 trial of
treatment with gefitinib in advanced, chemotherapy-refractory non–small-cell lung cancer was the first to show that patients with FISH-positive tumors had significantly higher rates of response and survival than patients with FISH-negative tumors. In the BR.21 trial, patients with FISH-positive tumors (approximately 40% of the patients) who were randomly assigned to receive erlotinib had significantly longer survival as compared with patients with FISH-positive tumors who received placebo. In the patients with FISH-negative tumors, there was no significant difference in survival. Similar results were observed in the ISEL trial, which confirmed that patients with FISH-positive tumors who were treated with gefitinib had higher response rates and longer survival than patients receiving placebo. No difference in survival was seen in FISH-negative patients, irrespective of treatment. However, FISH analysis failed to demonstrate any difference in progression-free survival or overall survival in a phase 3 trial that compared gefitinib with docetaxel as second-line therapy for advanced non–small-cell lung cancer (the Iressa Non–Small-Cell Cancer Trial Evaluating Response and Survival against Taxotene [INTEREST]).

The predictive role of increased EGFR copy numbers has also been evaluated in patients with metastatic colorectal cancer in a series of retrospective studies. The first report on the correlation between positive results for EGFR and a response to therapy with cetuximab or panitumumab involved a small cohort of patients (31 patients) with advanced, chemotherapy-refractory colorectal cancer. Recently, a FISH analysis of EGFR in tumor samples from patients enrolled in the phase 3 study comparing the use of panitumumab with best supportive care was reported. In the group treated with panitumumab, patients with normal EGFR copy numbers had a shorter median progression-free survival and overall survival than patients with high EGFR copy numbers. Moreover, in the group treated only with best supportive care, no correlation between EGFR copy numbers and survival was observed, suggesting a predictive rather than a prognostic role of this genetic feature in patients with metastatic colorectal cancer who are treated with anti-EGFR monoclonal antibodies.

### Resistance to EGFR Antagonists

#### Intrinsic Resistance

Activating mutations in the K-RAS gene, which result in EGFR-independent activation of the mitogen-activated protein kinase pathway, are found in approximately 15 to 30% of patients with non–small-cell lung cancer and 40 to 45% of patients with colorectal cancer, and their presence generally correlates with a worse prognosis with respect to the outcome of the cancer. K-RAS mutations occur in patients with a history of substantial cigarette use. These mutations are most frequently recorded in codons 12 and 13 in the exon 2 of the K-RAS gene and are generally mutually exclusive with EGFR mutations. In several studies, K-RAS mutations have been significantly associated with lack of response to EGFR tyrosine kinase inhibitors in patients with non–small-cell lung cancer and with lack of response to cetuximab or to panitumumab in patients with advanced, chemotherapy-refractory colorectal cancer. Both findings suggest that EGFR-independent, constitutive activation of the K-RAS signaling pathway could impair the response to anti-EGFR drugs. However, no correlation between K-RAS mutations and efficacy was reported in the INTEREST trial, which compared docetaxel and gefitinib as second-line treatments for non–small-cell lung cancer. In contrast, the results of the phase 3 trial comparing the use of panitumumab with best supportive care in chemotherapy-refractory colorectal cancer have confirmed that the efficacy of panitumumab is limited to patients whose tumors carry the wild-type K-RAS gene.

#### Acquired Resistance

In patients with non–small-cell lung cancer that initially responds to gefitinib or erlotinib, an acquired resistance to EGFR inhibitors, resulting in treatment failure, is associated with the development of an additional EGFR mutation. The most extensively studied of such EGFR mutations occurs in exon 20, resulting in a substitution of methionine for threonine in codon 790 (T790M). This mutation causes a change in the tridimensional structure of the tyrosine kinase domain and prevents both erlotinib and gefitinib from binding to EGFR. According to a recent report, amplifi-
cation of the MET proto-oncogene could be involved in acquired resistance to EGFR tyrosine kinase inhibitors in patients with non–small-cell lung cancer.\textsuperscript{104} MET amplification leads to EGFR-independent activation of the PI3K–AKT pathway through activation of HER3-dependent signaling. In a gefitinib-sensitive lung-cancer cell line that developed resistance to gefitinib as a result of MET amplification, inhibition of MET signaling restored sensitivity to gefitinib.\textsuperscript{104} A pilot study of 18 tumor specimens from patients with non–small-cell lung cancer that had previously responded to gefitinib but that subsequently developed clinical resistance showed MET amplification in 4 of the tumors.\textsuperscript{104}

**Future Directions**

Appropriate selection of patients is a major challenge for the clinical use of EGFR antagonists. In fact, although long-lasting therapeutic responses have been observed even in patients with heavily pretreated, metastatic cancer, responses are observed in only 10 to 20\% of patients receiving these drugs.\textsuperscript{105} Cancer cells must express functional EGFRs to respond to these agents. An optimal response to EGFR antagonists also requires the EGFR-activated intracellular signal-transduction machinery to be intact. In addition, EGFR-dependent cancer cells may escape from EGFR-targeted growth inhibition by using alternative growth factor receptor pathways or by constitutively activating downstream intracellular signaling effectors,\textsuperscript{106–109} indicating the need for therapeutic strategies designed to overcome resistance to EGFR inhibitors.\textsuperscript{110–112} Several molecular predictors have been detected for identifying patients who would be most likely to benefit from treatment with anti-EGFR drugs. However, most available clinical data are from retrospective studies and subgroup analyses; there is an urgent need to validate these observations in properly designed prospective studies. Another clinical issue is the need to determine the most effective sequences and combinations of EGFR inhibitors to use with chemotherapy, radiotherapy, or both in order to optimize cytotoxicity potentiation. In fact, the schedules that have been tested so far have been based on the empirical association of a standard chemotherapy regimen with the continuous administration of an EGFR-targeting drug rather than derived from molecular, pharmacokinetic, and pharmacodynamic studies.

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42. Bezjak A, Tu D, Rubin M, Hochster H, et al. Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11-refractory...
colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR).


The current era of research in antiangiogenic therapy for cancer began in earnest in 1971 with the publication of Folkman's imaginative hypothesis, but 33 years would elapse before the first drug developed as an inhibitor of angiogenesis was approved by the Food and Drug Administration (FDA). This approval was based on the survival benefit observed in a randomized phase 3 trial of first-line treatment of metastatic colorectal cancer; in that trial, bevacizumab, a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), was combined with conventional chemotherapy. Bevacizumab therapy also increased overall survival in the first-line treatment of advanced non–small-cell lung cancer when used in combination with standard chemotherapy. Two other antiangiogenic drugs, sorafenib and sunitinib, have also been approved by the FDA; these are oral small-molecule-receptor tyrosine kinase inhibitors (RTKIs). They target multiple receptor tyrosine kinases, including VEGF receptors and platelet-derived growth factor (PDGF) receptors. Sorafenib and sunitinib have been beneficial in the treatment of metastatic renal-cell cancer when used alone. Sorafenib monotherapy is also active in the treatment of hepatocellular carcinoma and was recently approved by the FDA for this indication.

The survival benefits of these treatments are relatively modest (usually measured in months), with the possible exception of the benefits for patients with renal-cell carcinoma. These treatments are also costly and have toxic side effects. These concerns raise the following questions with respect to improving antiangiogenic therapy: How do such drugs work, and how does bevacizumab increase the efficacy of chemotherapy? Several theories have been postulated, including the theory that antiangiogenic drugs improve chemotherapy by causing “vessel normalization” in tumors (see Appendix 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). How do tumors become resistant to antiangiogenic drugs? Are there clinically useful markers that can predict the efficacy of this class of drug? Are there promising surrogate pharmacodynamic biomarkers that will help to determine the best dose of a particular agent? Will antiangiogenic RTKIs such as sunitinib or sorafenib consistently enhance the efficacy of chemotherapy? What accounts for the side effects of these agents?

Many recent discoveries have the potential not only to answer some of these questions but also to indicate new therapeutic targets and treatment strategies. The purpose of this review is to summarize a number of these discoveries, made mainly over the past 5 years, and to point out their potential clinical impact.

THE VEGF AND VEGF-RECEPTOR FAMILY IN TUMOR ANGIOGENESIS

Much attention has been focused on the VEGF family of growth factors and the receptor tyrosine kinases that mediate their proangiogenic effects (Fig. 1). This family of structurally related molecules includes VEGF-A, VEGF-B, VEGF-C, VEGF-D,
and placental growth factor (PLGF). The major mediator of tumor angiogenesis is VEGF-A, usually referred to as VEGF. VEGF signals mainly through VEGF receptor 2 (VEGFR-2), which is expressed at elevated levels by endothelial cells engaged in angiogenesis and by circulating bone marrow–derived endothelial progenitor cells. The role of VEGF receptor 1 (VEGFR-1) is a mystery with respect to VEGF-mediated angiogenesis. It binds VEGF with approximately 10 times the affinity of VEGFR-1 and also produces VEGF indicates that VEGFR-1 may be expressed not on the surface of the tumor but rather within the cell, where they promote cell survival by an “intracrine” mechanism; this effect is mediated through the hypoxia-inducible transcription factors 1α and 2α.

Most types of human cancer cells express VEGF, often at elevated levels; this is a likely consequence of the numerous and diverse genetic and epigenetic ways in which VEGF can be induced (Fig. 1). Hypoxia, a characteristic of solid tumors, is an important inducer of VEGF. Its effect is noted through the hypoxia-inducible transcription factors 1α and 2α.

It is commonly held that VEGF action is attributable to a paracrine mechanism by tumor cells—that is, tumor cells produce VEGF but cannot respond to it directly since they do not have cell-surface VEGF receptors. In contrast, endothelial cells engaged in angiogenesis express numerous VEGF receptors, but they produce very little or no detectable VEGF. It is now clear, however, that VEGF in amounts sufficient to drive tumor angiogenesis originates from various host cells in the body such as platelets and muscle cells; such cells also include tumor-associated stromal cells. These findings explain, at least in part, why elevated VEGF levels in blood or even tumor tissue do not predict a benefit in patients receiving drugs that target the VEGF–VEGFR-2 pathway. The observation that tumor cells of many types express VEGF receptors (especially VEGFR-1) and also produce VEGF indicates that VEGF may sometimes act as a direct (cell-autonomous) autocrine growth factor for tumor cells. Furthermore, in some cases the VEGF receptors may be expressed not on the surface of the tumor cell but rather within the cell, where they promote cell survival by an “intracrine” mechanism; this has been shown for VEGFR-1 in breast-cancer cells. Hematopoietic stem cells also express both intracellular VEGFR-1 and VEGF, which can in some instances promote the growth and survival of these cells.

Results in mice bearing a mutant VEGF gene only in vascular endothelial cells suggest that very low levels of autocrine-acting VEGF mediate endothelial-cell survival and vascular homeostasis by signaling through intracellular VEGFR-2. Such mice have severe cardiac defects and are subject to gastrointestinal perforations and thrombotic
events; these adverse effects are sometimes observed in patients treated with bevacizumab.\textsuperscript{11,12}

These observations have potential clinical implications with respect to the use of small-molecule antiangiogenic RTKIs or monoclonal antibodies.\textsuperscript{30,31} The RTKIs, by virtue of their ability to penetrate cells, could cause certain toxic side effects,\textsuperscript{31} such as myelosuppression (which can also be caused by targeting other receptor tyrosine kinases such as c-kit and fms-like tyrosine kinase 3), but they may also be more effective than antibodies when used to treat tumors with functional intracellular autocrine VEGF receptors.

There is growing evidence of the role, under certain circumstances, of neuropilins in tumor angiogenesis.\textsuperscript{32,33} These transmembrane receptors lack tyrosine kinase activity, bind semaphorin 3A, and are normally involved in axon guidance. However, neuropilins also bind VEGF\textsubscript{165}, a splice variant of VEGF-A, and thereby modulate angiogenesis\textsuperscript{32,33}; they can act as coreceptors for VEGF-R2. Consequently, neuropilins are emerging as potentially promising antiangiogenic targets.\textsuperscript{34}

Another advance is the development of monoclonal antibodies to PlGF,\textsuperscript{35} a growth factor that binds to VEGFR-1. These antibodies have few side effects in mice because PlGF, unlike VEGF, is expressed minimally or not at all by most normal cells and tissues.\textsuperscript{35} Moreover, anti-PlGF antibodies can act in concert with antibodies targeting the VEGF pathway of tumor angiogenesis.\textsuperscript{35}

Circulating VEGF and a soluble form of VEGFR-2
have been used as surrogate markers of antiangiogenic drug activity. The measurement of these molecules in blood has been used as a preclinical means of establishing the optimal biologic dose of drugs that target VEGFR-2, including antibodies and small-molecule RTKIs. Such drugs can cause dose-dependent alterations in the levels of circulating VEGF or soluble VEGFR-2, and in mice these levels correlate with antitumor activity. The assessment of circulating VEGF in a complex with a VEGF antagonist such as the soluble “decoy” receptor drug called the “VEGF trap” (aflibercept) is also a promising approach for predicting the blockade of angiogenesis.

Another receptor tyrosine kinase signaling pathway is mediated by tie-2, a receptor tyrosine kinase expressed principally on the vascular endothelium. There are two major ligands for tie-2, angiopoietin-1 (ang-1) and angiopoietin-2 (ang-2). Ang-1 acts as an agonist, whereas ang-2 acts as an antagonist, but it can promote angiogenesis, especially in cooperation with VEGF. These angiopoietins act in concert with VEGF to stabilize and mature new capillaries. Blockade of this tie-2 pathway has been more difficult than blockade of the VEGF pathway, in part because of the complexity of agonistic and antagonistic ligands for the same receptor and the problems in finding effective and specific drugs against tie-2 or the angiopoietins. However, antibodies and peptidemlike antibodies (“peptibodies”) against ang-2 have recently been developed; these can block tumor angiogenesis and tumor growth in preclinical models.

Research on this signaling system has also highlighted the importance of the pericyte, an accessory cell that is closely associated with blood vessels. Not only endothelial cells but also pericytes secrete ang-1. Moreover, pericytes express PDGF receptors, which may be relevant to the antiangiogenic effects of certain small-molecule RTKIs that target PDGF receptors.

Studies have implicated what appears to be a pivotal new angiogenesis signaling pathway, notch–deltalike ligand (Dll) 4. Notch cell-surface receptors (i.e., notch 1, 2, 3, and 4) are expressed by various cell types and are generally involved in cell fate, differentiation, and proliferation. These receptors interact with transmembrane ligands (jagged 1, jagged 2, and Dll1, Dll3, and Dll4) on adjacent cells. Vascular endothelial cells express notch 1 and notch 4 receptors and the jagged 1, Dll1, and Dll4 ligands; among these, Dll4 is expressed exclusively by endothelial cells. Experiments involving gene disruption in mice have shown that notch–Dll4 signaling is essential for vascular development in the embryo. The combined use of an anti-VEGF drug and a Dll4-targeting drug can be more effective than either drug used alone, and tumors that are resistant to an anti-VEGF drug can be treated with a Dll4-targeting drug.

This finding may suggest that the notch–Dll4 signaling system is a major stimulator of angiogenesis and could be an appealing drug target, since Dll4 is up-regulated in the tumor vasculature, in part by VEGF. Paradoxically, drugs that target Dll4, including neutralizing antibodies, actually increase tumor angiogenesis, but most of the newly formed blood vessels are abnormal and functionally compromised in ways that drastically reduce blood flow. As a result, tumor hypoxia is
increased by up to seven times the normal level, thereby retarding tumor growth. Apparently, angiogenesis induced by VEGF up-regulates Dll4 in the endothelial cells of developing blood vessels and in doing so allows Dll4 to act as a negative feedback mechanism to prevent an excess of chronic, functional angiogenesis. Another mechanism that inhibits excessive angiogenesis involves vasohibin, a protein in activated endothelial cells that is induced by stimulators of angiogenesis such as VEGF. Vasohibin is thus a specialized member of a large and growing number of endogenous angiogenesis inhibitors such as angioatin, endostatin, thrombospondin-1, and tumstatin. The therapeutic potential of anti-Dll4 drugs is an issue of considerable interest. The question of whether they need to be combined with chemotherapy, radiation therapy, or other antiangiogenic drugs is important, because a therapy that induces
such profound vessel dysfunction in tumors and elevated levels of tumor hypoxia could be counterproductive when added to radiation therapy or chemotherapy. On the other hand, the increase in proliferating endothelial cells induced by anti-Dll4 drugs could result in a more potent vascular targeting effect mediated by chemotherapy and perhaps radiation therapy.

**Angiogenesis and Circulating Bone Marrow–Derived Cells**

Many cell types can be mobilized from the bone marrow and can home to sites of new blood-vessel formation, where they amplify the angiogenic process\(^2\) (Fig. 3). These cells include various hematopoietic-cell (CD45+) populations, many of which are monocytic or myeloid cells that express such endothelial-cell markers as VE-cadherin, VEGFR-1, VEGFR-2, and tie-2.\(^{53-57}\) They also express chemokine receptors such as CXC chemokine receptor 4 (CXCR4), which binds stromal-cell–derived factor 1 (SDF-1, also called CXCL12), a chemokine that attracts lymphocytes and certain other cell types. Neutrophils\(^{58}\) and macrophages\(^9\) can also have proangiogenic properties. In addition, there is a nonhematopoietic (CD45–) bone marrow cell population, the circulating endothelial progenitor cells. In contrast to perivascular cells, which function through paracrine mechanisms such as local secretion of VEGF,\(^{57}\) circulating endothelial progenitors are thought to merge with the wall of a growing blood vessel, where they differentiate into endothelial cells\(^{60}\) (Fig. 3).

The study of circulating endothelial progenitors has generated considerable interest and controversy.\(^{72}\) The various cell-surface markers used to describe such cells (which can be expressed by other cell types) and the methods used to detect them probably contribute to the widely divergent reports of the levels of incorporation of these cells into new blood vessels\(^2\); these levels range from highs of 20 to 50% or more\(^{64,62}\) to lows of 5% or less,\(^{52,63}\) the lower levels being more common. These differences have cast doubt on the general role of circulating endothelial progenitors in tumor angiogenesis, but in virtually all studies of these cells in tumors, untreated tumors were analyzed, or, as in one clinical study, the treatment was completed long before the tumors were analyzed.\(^{65}\) In contrast, in preclinical studies, acute and marked mobilization of the progenitors from the bone marrow has been shown to occur immediately after treatment with vascular disrupting agents (VDAs).\(^{64}\) These potent drugs, mostly microtubule inhibitors, can rapidly shut down the abnormal tumor vasculature, thereby causing massive tumor hypoxia and necrosis.\(^{65,66}\) Invariably, a viable rim of tumor tissue remains;\(^{65,66}\) Within hours after VDA treatment, the number of circulating endothelial progenitors increases, and they invade and colonize the viable rim of the tumor, thereby contributing to the rapid regrowth of the tumor.\(^{64}\) However, this process can be blocked by an anti–VEGFR-2 antibody.\(^{64}\) In addition to their role in VDA treatment, the contribution of circulating endothelial progenitors may be critical during the very early stages of the development of a tumor, but the population of these cells in the vasculature is progressively diluted by differentiated endothelial cells.\(^{67}\) Furthermore, the incorporation of relatively few endothelial progenitor cells (e.g., approximately 12%) into new blood vessels can have major promoting effects on functional tumor growth such as the progression of microscopic metastatic lesions to macroscopic ones.\(^{68}\)

The contribution of circulating bone marrow–derived cells to angiogenesis has a number of clinical implications. For example, a chemotherapy drug such as cyclophosphamide, administered at maximum tolerated doses, can mobilize circulating endothelial progenitors,\(^{69,70}\) which could conceivably contribute to regrowth of the tumor. Conversely, the closely spaced, regular administration of relatively less toxic doses of chemotherapy drugs, with no prolonged breaks — metronomic chemotherapy\(^71\) — can prevent mobilization of circulating endothelial progenitors and can act against not only the endothelial progenitors\(^72\) but also differentiated endothelial cells in the tumor neovasculature.\(^73,74\) Several clinical trials of metronomic chemotherapy are ongoing (Appendix 2 of the Supplementary Appendix).\(^75\)

The use of hematopoietic growth factors in patients with cancer who receive high-dose or dose-dense chemotherapy merits consideration here because recombinant granulocyte colony-stimulating factor (G-CSF) can mobilize not only endothelial-cell progenitors,\(^76\) but also CD11b+ granulocyte differentiation antigen (Gr1)+ myeloid suppressor cells that can promote angiogenesis\(^77,78\) (Fig. 3). In preclinical studies, the number of mobilized progenitors can be used as a surrogate pharmacodynamic marker to help establish
the optimal dose of metronomic chemotherapy, and enumeration of apoptotic circulating endothelial cells has been used to predict anti-angiogenic drug activity induced by metronomic chemotherapy. However, these methods remain to be validated in larger prospective clinical studies. Finally, since many of the cells shown in Figure 3 express VEGFR-1 and CXCR4, there are prospects for using drugs that target these receptors to inhibit angiogenesis mediated by relevant bone marrow–derived cells.

**Resistance to Antiangiogenic Drugs**

Intrinsic resistance and acquired resistance to antiangiogenic drugs are clinically significant problems. Preclinical studies have begun to shed light on the mechanisms of such resistance. With respect to intrinsic resistance, it has been shown that a tumor cell line from mice that is resistant to anti-VEGF antibodies becomes colonized by bone marrow–derived cells (CD11b+Gr1+ myeloid-suppressor cells) when transplanted into mice. Moreover, when normally sensitive tumor cells are mixed with these cells that are resistant to anti-VEGF antibodies and transplanted into other mice, the transplanted tumors resist anti-VEGF antibodies. Intrinsic resistance can also occur as a result of tumor cells using existing blood vessels in vasculature-rich organs such as the lungs, or simply as a result of the absence of VEGF or VEGF receptors in metastatic tumors growing in certain organ sites when drugs that target the VEGF pathway are used.

Acquired resistance to anti-VEGFR-2 antibodies can be caused by the redundancy of angiogenesis stimulators. An example is the up-regulation...
of the angiogenesis stimulator basic fibroblast growth factor (bFGF) within the tumor after treatment with anti–VEGFR-2 antibody therapy; this effect is probably caused by the elevated levels of hypoxia induced by the drug treatment.\textsuperscript{87} Clinically, treatment with bevacizumab increases circulating PlGF, which could cause drug resistance.\textsuperscript{88} In humans, sunitinib can induce high levels of circulating PlGF and VEGF that revert to normal levels during drug-free periods; these results can be reproduced in mice, but the presence of a tumor is not necessary for the effect.\textsuperscript{36} G-CSF and SDF-1, which can mobilize circulating endothelial progenitors\textsuperscript{52,76} and possibly other proangiogenic accessory cells,\textsuperscript{57} are also up-regulated in healthy mice treated with sunitinib. Moreover, it is possible that two or more such induced growth factors\textsuperscript{89} could act in a synergistic manner to promote tumor angiogenesis, as has been shown for bFGF and an isoform of PDGF.\textsuperscript{90} Such effects could contribute to rapid vascular regrowth in tumors after discontinuation of certain antiangiogenic treatments.\textsuperscript{90}

Acquired resistance can also develop through the selection and overgrowth of mouse tumor cells with mutations in genes such as Tp53, which cause relative resistance to hypoxia.\textsuperscript{91} These variants may be less dependent on the oxygen supplied by the newly formed blood vessels than are tumor cells without the mutations.\textsuperscript{91} Rapid vascular remodeling of tumor-associated vessels as a consequence of antiangiogenic therapy is another cause of resistance.\textsuperscript{92} The mature remodeled vessels are resistant to antiangiogenic drugs, which usually target relatively immature vessels.\textsuperscript{93} These aforementioned mechanisms suggest various possible strategies to delay or possibly even reverse acquired resistance.\textsuperscript{87}

**Angiogenesis and Cancer Stem Cells**

Studies have identified in tumors a minor population of cells with the characteristics of “tumor-initiating” cancer stem cells.\textsuperscript{94–96} These cells are thought to drive tumor growth and to constitute the seeds of resistance to treatment. The cancer stem-cell hypothesis is based largely on the results of transplantation of selectively enriched populations of cells into immunodeficient mice. Transplantation of extremely small numbers of such putative human cancer stem cells results in a high rate of tumor “takes,” whereas transplantation of much larger numbers of cancer cells lacking stem-cell characteristics does not.\textsuperscript{94,95} It has been suggested that conventional chemotherapy and other types of drugs attack the latter cells but not the cancer stem cells.\textsuperscript{96} The potent tumorigenic properties of cancer stem cells suggest that they may be strongly proangiogenic, and there is some evidence of this feature,\textsuperscript{97} which may help to explain some of the effects of tumor-inhibiting antiangiogenic drugs.

In addition, putative cancer stem cells in brain tumors reside in close proximity to blood vessels in a “vascular niche.”\textsuperscript{98} Treatment of orthotopic transplanted gliomas in mice with antibodies to VEGF disrupts the vascular niche and targets the stem-cell population.\textsuperscript{98} This population expresses high levels of VEGF and thus would be expected to be sensitive to anti-VEGF treatment.\textsuperscript{98} Low-dose metronomic chemotherapy may target the population of cancer stem cells or cells that are like cancer stem cells,\textsuperscript{99} especially when it is combined with an antiangiogenic drug such as anti–VEGFR-2 antibodies.\textsuperscript{74}

**Summary**

The increasing use of antiangiogenic drugs for the treatment of cancer has emerged from decades of extensive basic and clinical research. The clinical benefits of such drugs, however, are relatively modest. Improvements are likely to come from a more thorough understanding of the molecular and cellular mechanisms governing tumor angiogenesis and the response to antiangiogenic therapies. A number of recent advances promise to bring about such improvements. These include new findings in the VEGF and the VEGF-receptor family, discovery of the notch–Dll4 signaling pathway in tumor angiogenesis, elucidation of the proangiogenic role of circulating bone marrow–derived cells, identification of the mechanisms of resistance to antiangiogenic drugs, and observations that suggest a role of angiogenesis in the survival and growth of cancer stem cells.

Many of these discoveries and others suggest strategies for improving the clinical benefits of antiangiogenic therapy. These strategies include the development of better preclinical models to study the biology of tumor angiogenesis and antiangiogenic therapies (see Appendix 3 of the Supplementary Appendix). Such improvements will
also be critical in the use of long-term antiangiogenic therapy in the adjuvant setting in patients with early-stage disease. With respect to the treatment of metastatic disease, the magnitude and diversity of targets for antiangiogenic approaches suggest numerous possibilities for antiangiogenic drug combinations that should be much more effective than monotherapy in treating cancer.

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REFERENCES


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After completion of this CME activity, health care providers should be able to:

- Outline how oral chemotherapy is financed and how payment issues for oral chemotherapy may differ from those of parenteral chemotherapy
- Recognize the common misperceptions about oral chemotherapy and discuss these with patients
- Utilize patient selection criteria for oral chemotherapy regimens
- Summarize the impact that widespread use of oral chemotherapies may have on oncology practice

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NCCN Task Force Report

NCCN Task Force Report: Oral Chemotherapy

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Approved in the 7 months between December 2005 and July 2006. Lapatinib and nilotinib were approved in 2007. Experts anticipate that this trend will continue in the coming years. They further estimate that more than one quarter of the 400 antineoplastic agents now in the pipeline are planned as oral drugs.

Compared with the oral chemotherapy drugs available before 1996, these newer drugs, consistent with their parenteral contemporaries, are considered costly. For example, the estimated yearly cost of lenalidomide for a patient with multiple myeloma is $74,000, and, depending on dosage, the yearly cost of imatinib for patients with chronic myelogenous leukemia (CML) ranges from $29,000 to $57,000. Imatinib accounts for the largest percentage of spending on oral chemotherapy, ranging from 29% to 39%, depending on whether pharmacy benefits are provided by an insured health plan or self-insured employer. The availability of these new drugs has had an immediate impact on pharmacy budgets. Spending on oral chemotherapy drugs, while still a small proportion of total pharmacy benefit costs, has more than doubled between 2002 and 2006, from 0.3% to 0.7%.

Anticancer agents, including oral drugs, can be broadly categorized as chemotherapy, which in the past generally referred to cytotoxic agents, and biologic therapy, which generally referred to therapy targeted specifically at cell surface proteins or pathways that are relatively specific to cancer biologic pathways. Biologic therapy is also often referred to as targeted therapy. However, chemotherapy has also been used as an inclusive term encompassing all antineoplastic therapies, and the distinctions between targeted and non-targeted and biologic therapy versus chemotherapy would, at this time, appear to be somewhat artificial. In this discussion, the term chemotherapy is used generally to describe both cytotoxic and biologic therapy.
Drivers of Oral Chemotherapy

In the past, developers of new anti-cancer therapies focused primarily on parenteral drug delivery, in part because this route bypassed the variable absorption patterns of the gastrointestinal tract. For example, oral drugs must be stable in the low pH environment of the stomach but also must dissolve in the small intestine where the drug is absorbed. Additionally, interaction with other substances in the gastrointestinal tract, such as food or other drugs, must be considered, as must the first pass effect on the liver.

In contrast, parenteral administration was considered relatively straightforward and compatible with the cytotoxic action of most chemotherapies. Cytotoxic chemotherapy regimens are designed to deliver the maximal tolerated dose of chemotherapy to optimize cell kill in a single episode, followed by a several week period to allow bone marrow recovery. This episodic administration lends itself to the parenteral route. In fact, the operational and financial infrastructure of oncology practice has been based on the parenteral administration of chemotherapy. Oncology office visits and the configuration of office space have been centered on chemotherapy infusion, and oncologists derive a substantial portion of their income from supplying and administering parenteral chemotherapy.

Oral chemotherapy is changing this model. Many current anti-cancer therapies are primarily cytostatic in nature and thus are optimally effective when given chronically, so both tumor cells and the tumor microenvironment are continually exposed. This mechanism of action virtually requires oral daily therapy. Furthermore, the daily low-dose schedules often do not have the same dose-limiting side effects as high-dose intermittent schedules, making the cycling of regimens to allow for marrow recovery unnecessary.

Older paradigms used anticancer therapy for a limited number of cycles and then stopped. In contrast, many current therapies require prolonged treatment. For example, life-long imatinib therapy has revolutionized the treatment of CML and is an alternative to allogeneic stem cell transplantation.

New monitoring techniques for residual disease have also prolonged the duration of therapy. Before the availability of molecular monitoring of disease recurrence, the duration of treatment of some leukemias was based on the normalization of the peripheral blood or marrow. Now therapy may be continued if sensitive monitoring techniques detect minimal residual disease. These factors have prompted oncologists to reframe some cancers as chronic diseases requiring chronic therapy.

Imatinib therapy for CML is perhaps the best example yet of the promise of targeted therapies; the target is well defined and exquisitely sensitive to imatinib monotherapy. However, it is becoming apparent that this elegant simplicity is not typical of the more common epithelial malignancies. The complexity of the underlying pathobiology in colon cancer, for example, suggests that multiple different targeted therapies will be needed, both directed at the tumor cells themselves and the underlying tumor microenvironment. This suggests that there will be a growing market for the simultaneous use of multiple different targeted therapies.

The perception also exists that the standards for efficacy may be lower for targeted therapies. In fact, the standards for efficacy have been progressively lowering over the past several decades, but this process has more to do with the date of application than the mechanism of action of the agent involved. This difference in acceptable outcomes may also be related to the fact that targeted therapies are assumed to be less toxic, although the side effects of some biologic therapies can be quite significant.

For a number of reasons, pharmaceutical companies have invested heavily in the development of oral cancer drugs. One strong incentive is the introduction of Medicare Part D, which provides coverage for many oral chemotherapies for the first time. Research has been invested in both novel oral agents and also oral counterparts to existing cytotoxic therapies. For example, oral versions of docetaxel and topotecan are being developed. Experts suggest a market will exist for both oral and intravenous versions of many drugs. For example, in the new histone deacetylase inhibitors class of drugs (e.g., the recently approved vorinostat), both oral and intravenous agents are...
under development. For agents such as these, the choice between oral and intravenous administration may depend on physician and patient preferences and type of insurance coverage.

Common Misconceptions About Oral Chemotherapy
As the previous discussion shows, oral chemotherapy suggests a number of benefits. However, growing experience in administering these therapies suggests that a cautious approach is warranted. Clinicians should also understand the common misconceptions that may be contributing inappropriately to the enthusiasm for oral chemotherapy.

Patient Preference
Patient preference for oral chemotherapy has been one of the main drivers for its current popularity. Oral administration would seem to avoid many of the more objectionable aspects of parenteral therapy: the office visit and associated inconvenience of transportation and parking, time spent waiting in the office, and time lost during intravenous set up and infusion.

In 1997 Liu et al. reported on the results of a questionnaire addressing patient preference for oral versus intravenous palliative chemotherapy. Preference for route of administration was evaluated against diminishing treatment response. Of 102 assessable patients, 92 preferred oral chemotherapy and 10 preferred intravenous therapy. Not unexpectedly, the major reason given for preferring oral chemotherapy was convenience. However, although patients expressed a clear preference for oral chemotherapy, they were unwilling to sacrifice efficacy for this preference.

Although these results seem to support convenience as a driving factor for patient preference, at least in the palliative setting, this survey may have presented oral chemotherapy in an overly simplistic fashion. For example, the convenience of oral chemotherapy will only be realized if the patient is on an exclusively oral regimen. Patients on combination regimens will need to make office infusion visits anyway; for these patients, it may actually be more convenient to receive the entire regimen parenterally. Capecitabine, for example, is an oral alternative to 5-fluorouracil (5FU) that is often administered with other parenteral agents.

Additionally, patients may not realize that choosing an oral therapy over an intravenous equivalent will shift many of the responsibilities of managing the regimen and monitoring for doses and toxicity from the oncology team more directly to the patient. Although, some patients may appreciate a sense of empowerment from oral chemotherapy and get a sense of satisfaction from having direct responsibility for managing their chemotherapy, this same responsibility could become overwhelming, particularly for sick patients simultaneous dealing with complicated dosing regimens and schedules or for patients without reliable assistance from family or friends. The reliable administration of oral chemotherapy in the pediatric population is also challenging, even among well-intentioned families.

These advantages and disadvantages of oral chemotherapy must be carefully discussed with the patient. Only well-motivated and health-literate patients and families may be able to manage complex oral chemotherapy regimens, and only patients with good oral food intake, good gut function, and minimal nausea and vomiting will be good potential candidates.

Fewer Side Effects and Easier Administration
Patient preference for oral chemotherapy may be based on the incorrect assumption that oral therapy is associated with minimal side effects; some patients may incorrectly assume that oral chemotherapy is not “real” chemotherapy and is more akin to taking a vitamin or antibiotic. This dangerous misconception may also be the rationale for the preference of oral chemotherapy in frail elderly patients.

Patients must understand that oral equivalents of cytotoxic therapies, such as capecitabine, have side effects that are similar to their parenteral counterparts (in this case, fluorouracil). The need to monitor for side effects and titrate dosages increases the complexity of oral chemotherapy regimens. For example, many oncologists can relate examples of patients who began to experience toxicity from capecitabine on a Friday but who did not consult a physician over the weekend. If these patients continue on the same dosage, either because they do not recognize the incipient side effects or because they do not want to compromise the effectiveness of their chemotherapy, they may have a life-threatening level of toxicity by Monday.

Furthermore, from the patient’s perspective, an oral regimen may not be simple to administer. Instructions for capecitabine may include:
• Take with water within 30 minutes of a meal.
• If a dose is missed, do not take the drug when remembered and do not take a double dose.
• Stop taking capecitabine and contact the doctor if experiencing 4 or more bowel movements than usual per day, diarrhea at night, loss of appetite or large reduction in fluid intake, more than 1 vomiting episode in 24 hours, mouth sores, temperature greater than 100.5 °F, or pain, redness, or swelling of hands or feet that prevents normal activity.6

Oral regimens must also be integrated with non-cancer drug therapies taken for comorbidities. Oral chemotherapy regimens may be particularly difficult to manage in assisted living situations where drugs are dispensed by staff with limited experience in monitoring the side effects of chemotherapy.

Furthermore, supportive care agents such as the 5-hydroxytryptamine3 (5-HT3) antagonist antiemetic drugs are best used parenterally and intermittently. Reimbursement for these agents on a daily oral basis is often limited when pharmacy benefit management programs base reimbursement on the FDA-labeled indications. When all these requirements are considered, a periodic office visit to receive chemotherapy may be more attractive to patients.

Another common perception is that oral drugs have a broader therapeutic index and thus are safer than parenteral drugs. The therapeutic index is based on the class of drug and its mechanism of action, not the route of administration. Thus, the therapeutic index of oral agents versus intravenous counterparts is generally the same. Nevertheless, clinicians should note that although biologic agents are not cytotoxic in nature, the adverse effects associated with them can still be significant. For example, the skin rash and diarrhea associated with epidermal growth factor inhibitors can be debilitating.

In summary, the assumption that all patients will prefer oral agents or that all patients are appropriate candidates for oral therapies is overly simplistic. Furthermore, that oral chemotherapy is routinely preferable for frail, elderly, and less motivated patients is also a commonly held misconception. Generally, highly motivated, capable patients who want and can actively participate in their care are better suited to assume the increased responsibility that comes with chronic home oral administration of chemotherapy.

Certainly, for some regimens, oral chemotherapy is the only alternative. However, the example of imatinib monotherapy, a simple regimen with minimal side effects, may be the exception rather than the rule. An entirely oral chemotherapy regimen may offer significant advantages over traditional infusion therapy in carefully selected patients, but patients must understand that the decision to use oral chemotherapy requires detailed consultation with the oncologist and oncology team, as well as ongoing support over the course of therapy.

Cost of Oral Chemotherapy: Offset by Decreased Need for Support Staff or Infusion Centers?

Some have argued that the high cost of oral chemotherapy drugs may be offset by the decreased need for ancillary services, particularly oncology nursing staff and infusion centers. Experience, however, has not uniformly borne this out. Oral chemotherapy requires a significant amount of nursing time for patient education when starting an oral chemotherapy regimen and extensive telephone consultation thereafter. Furthermore, in most practices, no time is built in for counseling patients on oral chemotherapy, and most offices do not have any dedicated space or personnel for this counseling. Thus, education and counseling have been improvised in hallways and other less private settings. Some oncologists offer written material, video material, or group educational sessions, but the bottom line is that the extensive and ongoing patient education required to ensure safe and effective oral chemotherapy is uncompensated and perhaps underappreciated. In contrast, prolonged infusion sessions provide many built-in opportunities for education.

Patient Selection Criteria for Oral Chemotherapy

Adherence

Although many patients may be eligible for oral chemotherapy, only a subset will both want to take oral agents and be considered appropriate candidates based on their ability to adhere to the regimen. One of the key factors in assessing candidacy for oral chemotherapy is adherence. Adherence can be a challenging commitment for many patients, and the decision to take oral chemotherapy must be based on a collaborative discussion between the patient and physician, with appropriate support from oncology staff.
In clinical trials of oral agents, adherence has generally been excellent except for selected populations (e.g., adolescents). However, in contrast with the clinical trial experience, adherence to chronic medication therapy in adult ambulatory care is generally fair to poor. Unfortunately, there is currently no well-established mechanism to prospectively assess adherence. For example, approximately 50% of patients taking statin drugs will discontinue taking the medication within 6 months.

Patients with cancer are believed to be particularly motivated to adhere to chemotherapy regimens. In fact, occasional overadherence can pose health risks. Nevertheless, studies have shown that nonadherence to oral chemotherapy is still an issue.

For example, imatinib is a very effective oral agent; it has an uncomplicated daily regimen and few major side effects. The drug is considered life-saving for patients with CML, converting a universally fatal disease into a manageable chronic one. Given these factors, one might expect a near 100% adherence rate. However, studies have not borne this out. Tsang et al. analyzed pharmacy claims data to determine prescription adherence and persistency of 4043 patients receiving imatinib over 24 months. Overall compliance (defined as apparent mg taken/mg prescribed) was 75%, and only 50% of patients were 100% compliant. Persistency (time on therapy without significant gaps in refills) averaged 255 days over 24 months. Although adherence and persistency in this study may be superior to those seen with nononcology medications, suboptimal adherence with daily imatinib may compromise treatment effectiveness.

Partridge et al. reviewed the literature regarding adherence to oral chemotherapy. Most studies examined adherence in the context of a clinical trial, which probably represents the optimal situation of highly motivated and supervised patients. However, even in this setting, adherence was variable, ranging from less than 20% to almost 100%.

Assessing adherence to parenteral therapy is straightforward; physicians know exactly how much chemotherapy was given over what period of time and on which day. This level of control is not possible with oral chemotherapy, where there is shared responsibility for ensuring that prescriptions will be filled, that the patient will promptly initiate the drug therapy at the correct time of day at the correct dosage, or that the patient will alert the clinician of adverse symptoms in a timely way. Payor information systems can capture whether or not the prescription is filled, but anecdotes abound of patients who have shoeboxes full of unused prescriptions. In addition, few innovations have been developed in oncology care to help support safe and reliable administration of oral chemotherapy. Lessons for disease management programs in asthma and depression management may offer helpful lessons for oncology.

Studies have shown that adherence is related to sociodemographic characteristics, type of regimen (i.e., side effects and duration), and characteristics of the illness (i.e., symptoms and seriousness). However, predicting how these parameters interact with each other and determining how they can be used to predict adherence is difficult.

Table 1 summarizes factors often associated with nonadherence to oral regimens and lists factors that may help oncologists identify patients who need specialized or targeted interventions to support the reliable use of oral chemotherapies.

### Table 1: Factors Associated With Nonadherence to Oral Regimens

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
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<tr>
<td>Complex treatment regimens</td>
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<tr>
<td>Substantial behavior change required</td>
<td></td>
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<tr>
<td>Inconvenient or inefficient clinics</td>
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<tr>
<td>Inadequate supervision</td>
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<tr>
<td>Poor communication with health care providers</td>
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<tr>
<td>Patient dissatisfaction with care</td>
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<tr>
<td>Patient health beliefs in favor of nonadherence</td>
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<tr>
<td>Inadequate social support</td>
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<tr>
<td>History of nonadherence</td>
<td></td>
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<tr>
<td>History of mental illness</td>
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is another, more-cumbersome example of a direct method. However, this measurement can also be manipulated by the patient who becomes adherent just before an office visit. Additionally, requiring a blood sample to monitor oral therapy shows a certain irony.

A wide variety of indirect methods have been investigated, including, most obviously, questioning the patient about adherence. However, patient self-report may sometimes be unreliable because of either inaccurate recall or shame in admitting nonadherence. Other indirect methods include patient diaries, pill counts, rates of prescription refills, and electronic medication monitors. Of course, relatively simple methods as pill counts and prescription refills do not confirm adherence to the dosing schedule. A microelectronic monitoring system consisting of an “intelligent” tablet bottle can record the date and time of bottle openings. This approach has been used primarily in clinical trials, in which measuring adherence is critical. The expense of this approach limits its applicability to large scale use. Regardless of the technique used to assess adherence, clinicians must realize that lack of adherence typically reflects the complexity of the regimen rather than willful or manipulative behavior from the patient.

Uncertainty about patients’ ability to adhere to recommended treatments can create a therapeutic dilemma for the physician who is faced with a patient who appears to be nonresponsive to an oral drug. The physician cannot be certain if the lack of response represents true chemotherapy resistance or nonadherence. Similar to oral therapy in general, the inability to accurately confirm adherence has significant implications for investigating effectiveness and adverse events. Oncologists may need to contract explicitly with patients about oral chemotherapy adherence and to create a more elaborate infrastructure to support safe and reliable administration of oral chemotherapy.

**Safety Issues**

**Medication Errors**

Medication errors are a significant source of concern regarding the administration of chemotherapy. In recent years, a robust infrastructure of checks and balances has been implemented for the administration of parenteral chemotherapy, including templated orders, electronic order-entry systems with decision support, and clinician double-checks. In many academic institutions, every dose of chemotherapy is reviewed by at least 3 or 4 licensed health care providers. Key safety measures include checking calculations of such common parameters as dose per meter squared and estimate of body surface area. Written consent forms are used in some organizations for parenteral chemotherapy. Many comprehensive cancer centers have also developed standard order forms for a variety of chemotherapy regimens.

To date, however, fewer controls are built in for oral chemotherapy, so any presumed safety can only be characterized as hypothetical at present. For example, standard order forms generally do not exist for oral chemotherapy. Weingart et al. reported the results of a survey of 42 cancer centers in the United States regarding current safety practices for oral chemotherapy. The information required on a prescription, such as diagnosis, cycle number, any prescription double check by other clinicians, calculation of body surface area or dose per meter squared per body surface area, was variable. Ten of 42 responding cancer centers had no formal process for monitoring adherence, and 10 centers reported at least 1 serious adverse event in the prior year. The authors concluded that few of the safeguards routinely used for infusion chemotherapy had been adopted for oral chemotherapy at U.S. cancer centers.

Given these gaps in safeguards, the potential exists for a physician to write a prescription for an oral antineoplastic agent that is then filled at a local community pharmacy unfamiliar with oral chemotherapy or dosing schedules. In this possible scenario, the patient may not be given adequate instructions or understand the instructions for taking the chemotherapy, which may involve complicated cycles. The consequences of this scenario are potentially serious if, for example, a patient takes a drug that is intended to be taken weekly on a daily basis instead.

Drug interactions are another issue for all oral drugs. Pharmacy systems have built-in alerts to detect potential drug interactions, but the alerts are often perceived to be too sensitive and are overridden. Some systems may allow some alerts to be overridden, but in cases of serious potential risk, insist that the order/prescription be stopped until the pharmacist consults with the physician.

Specialty pharmacies (discussed further in a later section) may provide an additional level of safety checks, but the number of pills that a patient may receive with 1 prescription is still an issue. Capecitabine
Oral Chemotherapy

is one of the most common oral antineoplastic agents, and the policy in some academic centers is to limit a prescription to a maximum of 4 to 6 weeks of therapy. However, this safeguard is unlikely for drugs supplied by a mail order pharmacy. In addition, prescribing physicians may also lose patient contact if an extended supply of medication is given with a single prescription. This issue may be further aggravated if the patient is from out of town and does not routinely see the prescribing physician. Large employers have financial incentives to provide pharmacy benefits through mail-order pharmacies. The growing numbers of oral chemotherapeutics with potential serious side effects may prompt employers to rethink the balance between costs and potential safety issues when mail order pharmacies are used across the board.

Communication Issues

To prescribe oral chemotherapy safely, the clinician must take a comprehensive medication history. This can be challenging if clinicians do not elicit this information reliably or keep the medication list up to date by reconciling information about medications from various sources. The situation is improving under the Joint Commission requirement for “medication reconciliation” and with the use of electronic medical records and computerized order entry systems. In some organizations, clinicians can access information on drugs dispensed by pharmacies. Some payers can provide up-to-date dispensing histories, but these systems are not widely available or accessible. Other institutions’ dispensing information systems capture prescriptions filled within the particular hospital network, but do not provide information on drugs received through mail order or community pharmacies.

Adequate communication of side effects and toxicities is another key factor that may affect patient safety. Parenteral therapy provides opportunities for communication, particularly with nursing staff during therapy. Patients may be more comfortable detailing side effects and other concerns to support staff, but this kind of key interaction with nurses and other clinicians may not be available for patients receiving an entirely oral regimen. Therefore, additional communication channels and mechanisms may be necessary. These communication issues are similar to those associated with other complicated oral regimens for such common medical conditions as diabetes or asthma, although the potential for adverse events may be higher with oral chemotherapies.

The ability to monitor symptoms in real-time would help identify toxicities that may resolve by the next physician visit and consequently not be adequately recalled by the patient. Internet systems may improve communication for all patients. For example, patient-friendly web-based programs have been developed that allow patients to communicate chemotherapy toxicities in real-time either from home or in the oncologist’s office.

One such program is called the STAR program, which has been investigated in patients with lung cancer and gynecologic malignancies. Patients were encouraged to log in and report symptoms at each follow up or to access the system from home. In one study involving 80 patients with gynecologic cancer, 42 severe toxicities (grade 3–4) entered from home prompted 7 clinician interventions. Additionally, online self reporting of toxicity symptoms was shown to be feasible in 107 patients with lung cancer. Patients reported high satisfaction with the program, and the nurses who received the symptom reports felt that the information was useful for clinical decisions, documentation, and discussions.

Biohazard

Some 20 to 30 years ago, biohazards of chemotherapy were not appropriately recognized. Residents and interns could be found mixing doxorubicin solutions in a back office sink. Since that time, various workplace regulations have addressed the issue of occupational biohazards of parenteral chemotherapy; however, no such systems are in place for oral chemotherapy. Issues include whether or not oral chemotherapy should be placed in automatic pill counting machines and, if they are manually counted by the pharmacists, whether a dedicated counting tray should be used. Tablets will leave residue in the bottle and on the patient’s hand, an issue which may be most relevant for parents treating their children at home. These issues have not been well investigated for oral chemotherapy.

Oral Chemotherapy: Factors Affecting the Practice of Oncology

The large number of oral chemotherapies in the pharmaceutical pipeline prompts consideration of how the practice of oncology could change in the future.
Process of Care
The transition to oral chemotherapy may lead to a diffusion of direct patient care from the oncologist to a variety of individuals that the oncologist has no personal or financial relationship with or no direct supervisory role for. For example, specialty pharmacies participate in safety monitoring and some monitoring of chemotherapy side effects. Free-standing outpatient clinics, some run by pharmacists, may evolve to provide monitoring services for oncology patients. However, the oncologist still retains the ultimate responsibility for the patient’s care, and the expanding number of entities involved in cancer care management can make coordinating this care more challenging.

Oncology Offices and Infusion Centers
As noted, many oncology offices are set up to deliver parenteral chemotherapy, and the growing number of oral alternatives raises the potential problem of over-capacity. For the foreseeable future, however, this does not seem to be an issue. Cancer is primarily a disease of an older population, and given the aging of the U.S. population, the incidence of cancer is likely to grow. Although many novel cancer therapies provide only an incremental survival benefit, these new drug therapies may cumulatively result in a greater number of patients living for a longer period of time.

Even if the percentage of chemotherapy given as oral chemotherapy grows to 20% to 25% over the next decade, the most likely scenario is that oral chemotherapy will primarily be complementary to parenteral therapy. Whether oral therapy precedes, follows, or is used in combination with parenteral therapy, most patients will probably be treated parenterally at some point in their care. Thus, the bottom line is that oral chemotherapy is unlikely to substantially replace parenteral therapy at least for the next decade.

Oral chemotherapy may present a particular problem if a patient receiving oral therapy is admitted. The hospital must determine how to continue the oral chemotherapy while the patient is hospitalized: should patients bring the drugs to the hospital or should the hospital bear the uncompensated cost of providing the drugs? Continuing oral chemotherapy during an acute inpatient hospitalization has emerged as a complicated financial, ethical, and emotional issue.

Financial Impact
Oncology revenues in private practice have been largely based on the delivery of parenteral agents. In contrast, oncologists do not derive any revenue from oral chemotherapy independent of the fees received from office visits needed to monitor care. In addition, although oncologists generally receive payment for administering parenteral chemotherapy, no similar reimbursement is provided for administering oral chemotherapy.

Not surprisingly, research has suggested that financial constraints may play a role when a choice between oral and parenteral drugs is possible. For example, Jacobsen et al. analyzed the prescribing practices for chemotherapy according to type of physician reimbursement for treatment of Medicare beneficiaries with metastatic lung, breast, or colorectal cancers treated between 1995 and 1998. The study focused on the treatment of metastatic disease because a wide variety of chemotherapies are available in this setting without definitive evidence of one regimen’s superiority.

The authors found that providers who were more generously reimbursed prescribed more costly chemotherapy regimens. Frequently, the financial incentives of providers align with those of patients, who are trying to cope with a burdensome co-pay for oral therapy.

Other specialties face these same choices between oral and parenteral drugs. Rheumatologists and their patients, for example, must choose between 2 tumor necrosis factor inhibitors for the treatment of rheumatoid arthritis; infliximab (Remicade), which requires an IV infusion, and etanercept (Enbrel), which is self administered subcutaneously.

Distribution of Oral Chemotherapy
Prescriptions for oral chemotherapy can be filled in several ways: community pharmacies, mail order pharmacies, specialty pharmacies, hospital pharmacies, through the physician’s office as part of competitive acquisition programs (CAP), or through an office-based pharmacy that is legal in a number of states. Each of these distribution channels has different implications for the patient and physician.

Mail Order Pharmacies
Mail order pharmacies typically provide a minimum 90 day drug supply, which may represent thousands of dollars for oral cancer chemotherapy. The rationale behind a 90 day supply is that cost savings are available related to volume discounts and to eliminating
multiple dispensing fees. However, oral chemotherapy does not easily fit into the model of mail order pharmacy. For example, for safety reasons, hospital pharmacies frequently limit oral chemotherapies to a 30-day supply. Additionally, some oral chemotherapies require dose alterations, but these cannot be easily accommodated because mail orders typically include only 1 dosage. Additionally, patients do not have any opportunity to interact with a pharmacist, and this lost educational opportunity could impact the safety of oral chemotherapy.

**Specialty Pharmacies**

Specialty pharmacies were specifically designed to address the limitations of mail order pharmacies by focusing on a specific class of therapeutic drug that involved more complex management issues, a greater potential for harm, and more significant expense. Most often, patients take their prescriptions to their regular pharmacy, where the prescription is routed to a single vendor staffed by oncology pharmacists. The specialty pharmacist then calls the patient and discusses the therapy before shipping the drug.

In some programs, the specialty pharmacist will have access to the patients’ prescription medication records through payor information systems so that potential drug interactions can be anticipated. The oncology pharmacist can then call the physician for further discussion. Each drug may also have its own monitoring program, which notifies the pharmacist to call the patient within the time frame when common toxicities are expected. For example, the side effects of capecitabine therapy may be most severe in the first 4 days of therapy. Although these side effects will be identified by the specialty pharmacist, oncologists may not be informed by the monitoring program.

Specialty pharmacies are also more flexible in both the number and dosages of pills provided. Unlike mail order pharmacies, many impose 30-day limits on oral chemotherapies for safety reasons, but also to ensure that a subsequent refill is needed, thus avoiding waste. In addition, many can also provide a variety of dosages to accommodate needed dose alterations.

One potential source of confusion for patients is that they may receive drugs and information about appropriate use of those drugs from multiple sources. For example, drugs for hypertension may come from a mail order pharmacy, drugs for treatment of acute illness may come from a community pharmacy, and the oral chemotherapy may come from the specialty pharmacy.

Another challenge of specialty pharmacies is the insertion of an additional health care professional into the medical care of the patient, creating the need for further coordination. For example, patients can be confused if the information provided by the pharmacist is not consistent with that from the oncologist. Additionally, if the patient tells the pharmacist about adverse reactions, the pharmacist must then ensure that the information is relayed correctly to the oncologist and placed in the patient’s medical record. Few programs have robust mechanisms in place to ensure that information is communicated to (and received by) the appropriate parties. This can be a particular vexing challenge.

From the oncologist’s perspective, adding the pharmacist is an asset to the patient’s overall care as long as the pharmacy team is well integrated into overall care. Specialty pharmacies may be superfluous in a dedicated cancer center with large and active clinical pharmacy departments that already have sophisticated support strategies in place. In contrast, a specialty pharmacy system may be particularly helpful to smaller community practices with no other access to an oncology pharmacist.

**Hospital Pharmacies**

Hospital pharmacies associated with comprehensive cancer centers most often have similar capabilities to specialty pharmacies. For example, oncology pharmacists and nurses are often part of the health care team that reviews all medications and interacts with the patients. The comprehensive cancer center also interacts with satellite community pharmacies to provide the same services. In addition, an information system that records all the medications the patient receives through the parent hospital pharmacy is typically in place. However, the sophistication of the information systems is variable. Furthermore, information may be incomplete if some prescriptions are filled through specialty pharmacies or pharmacies outside the center network. In some institutions, almost half of the oral prescriptions are filled outside the network.

One exception is investigational therapies that are only provided through a hospital pharmacy. These oral drugs have a higher risk of adverse events and typically have a prescribing and tracking system that is independent of other routine oral agents.
Community Pharmacies
Depending on insurance coverage and set-up of the local hospital-based pharmacy, patients may access oral chemotherapy through a community pharmacy. For example, some hospitals may limit the availability of oral chemotherapy to investigational agents or patients with inadequate coverage, and mail order or specialty pharmacies may not be an option in some insurance plans. In this situation, the community pharmacy may order the drug for the patient, but the pharmacy staff may not have adequate experience to provide appropriate counseling. Some pharmacy chains may require counseling for some oral chemotherapy agents, but the quality and value of these consultations may be variable.

CAP
CAPs are a component of the Medicare Modernization Act (MMA) in which physician-owned clinics were offered the opportunity to acquire drugs for their Medicare patients from a CAP vendor. The CAP vendor assumes the risk of purchasing the drug, including the 20% co-pay from the beneficiary. The limitation of the CAP program is that the physician must acquire all drugs from the single vendor. Because of problems in administering the program and aligning economic incentives, very few physicians signed up, and CAP has not emerged as a major supplier of oral chemotherapy.

Financing Oral Chemotherapy
Medicare Part D
Medicare Part D, part of the MMA, profoundly changed the landscape of reimbursement for oral chemotherapy. Before Part D, the only oral chemotherapies covered by Medicare were a limited number of oral drugs with injectable counterparts covered under Medicare Part B, such as capecitabine. With Part D, cancer chemotherapy is now covered by 2 different components of Medicare: Part B for parenteral therapies and Part D for oral chemotherapies. This dual system can be very confusing to both patients and physicians.

In Medicare Part D, oral drugs are provided through either a prescription drug plan offering drug-only coverage or a Medicare Advantage Prescription Drug Plan (MA-PD), which offers both medical and drug coverage. Most patients have opted for a prescription drug plan, since it does not require them to change their existing medical coverage.

Both of these programs may use formulary and other management tools. The Centers for Medicare and Medicaid Services (CMS) review Part D plans’ formularies to ensure that they do not discriminate against beneficiaries with certain health conditions. One stipulation was the requirement that any Part D formulary include “substantially all members” of certain therapeutic classes of drugs, including anti-neoplastic drugs. The rationale for this policy was that a choice of therapies was more important in cancer treatment than in other illnesses; therefore virtually all oral cancer chemotherapies are included on formularies.

As originally set up, Part D has a $250 deductible and a 25% co-pay for the next $2000 in oral drug costs. Unfortunately, Part D also has a gap in coverage, referred to as the “donut hole,” and the patient is responsible for the next $2850 in drug costs. The particular levels that establish the 25% co-pay and the donut hole are indexed to inflation and adjusted on an annual basis. After the $2850 has been fully paid, the beneficiary is responsible for 5% of the remaining costs. This cycle starts again at the beginning of every calendar year.

Hundreds of different private insurance companies offer Part D plans with different co-pay rates and different deductibles. For example, some plans offer a version of the standard benefit that features a reduced deductible or flat co-payments instead of co-insurance. A 2006 analysis of Part D formularies found that both prescription drug plans and local MA-PDs cover 75% of cancer drugs, whereas regional MA-PDs cover 85%. No plans applied step therapy restrictions to cancer drugs.3

Although Medicare Part D does provide relief from catastrophic drug costs, the co-pays can still be burdensome, particularly given the high cost of oral chemotherapy. Medicare beneficiaries may qualify for a low income subsidy that reduces the cost-sharing burden, but this program is underused, perhaps because it adds one more form to an already complex process. Patients who cannot afford either the donut hole or co-pays may take their drugs intermittently or not at all.

These factors may affect the choice of oral versus parenteral chemotherapy. For example, patients starting chemotherapy toward the end of the year will promptly experience the large “donut hole” expense,
only to be faced with the same expense during the next year. Therefore, one could envision some patients choosing to start parenteral therapy and transition to oral therapy at the beginning of the next year.

Co-pays and co-insurance, although familiar aspects of medical care, are relatively new concepts for cancer chemotherapy. The idea of cost sharing is to expose the patient to the cost of therapy so that he or she can judge whether a treatment is worth the cost. Traditionally, patients with cancer have been shielded from this type of decision-making, and pharmacy benefits, at least for large employers, have not yet required high co-pays or co-insurance for cancer care. However, smaller employers may be considering these strategies as one way to make health insurance affordable for their employees.

Additionally, consumer-directed health plans and health savings accounts are other strategies to offer affordable insurance. Consumer-directed health plans typically combine a health plan with a high deductible and a health reimbursement arrangement (HRA) or health savings account (HSA). HRAs and HSAs are tax-advantaged accounts used to pay health care expenses. Balances can be used for future health use, potentially creating the incentive for enrollees to control their medical expenses.

High co-pays, co-insurance, or deductibles have an uncertain impact on chemotherapy use. Whether patients would choose to undergo additional chemotherapy for metastatic disease if the drug offered is associated with only an incremental benefit but a very high cost is unknown. This is a frequent situation in the use of biologic therapies to treat metastatic epithelial tumors.

Studies in non-oncology settings suggest that out-of-pocket expenses will affect therapy decisions. For example, Schneeweiss et al. studied adherence to statin therapy after myocardial infarction during 3 different time periods: when the statins were fully covered, with a co-pay, and with co-insurance. Although initiating therapy was not affected by coverage, the authors found that adherence was greatest with full coverage policies and that sudden changes to full out-of-pocket spending, similar to Medicare’s Part D donut hole, almost doubled the risk of patients stopping. Similar studies have not been done in the oncology setting, for either primary or adjuvant therapy. However, given the gravity of a cancer diagnosis, many oncologists report that patients are unlikely to interrupt primary therapy if at all possible, and seek other funding, such as second mortgages on their homes.

Avoiding co-pays can affect prescribing practices in other ways. For example, sunitinib comes in 3 strengths, 12.5, 25, and 50 mg tablets. The starting dose is typically 50 mg, and dose reductions are not unusual. Therefore, physicians may prescribe the 12.5 mg tablets so that if dose adjustments are required, patients can avoid a separate prescription with a new co-pay. In this scenario, the patient must take 4 tablets instead of one to reach the starting dose of 50 mg. This type of maneuvering adds to the complexity of oral chemotherapy.

The array of Part D plans is confusing to patients and physicians alike, and physicians typically do not know what type of coverage patients have when planning treatment. Thus, they cannot anticipate the economic consequences. The assumption that most patients over age 65 have some sort of Medicare coverage is tempting, but many patients in that age range are covered by commercial plans based on prior employment. Conversely, patients under age 65 may have Medicare coverage based on other disabilities.

No easy mechanism is currently in place in the physician’s office to determine what type of coverage a patient has for oral chemotherapy. Making this determination can be time consuming, and further cost is added to the health care system when staff must make sure that the correct payment and co-payment have been received.

The Medicare donut hole also affects the revenue streams at hospital pharmacies. At the beginning of the year, hospitals may accumulate bad debt as patients are working their way through the donut hole. In contrast, revenue is more secure in subsequent months as Medicare Part D assumes coverage for most of the costs. To compensate for this shortfall, hospital pharmacies must increase their charges in subsequent years, thus creating a vicious cycle. Some hospitals have adopted the policy of continuing treatment for patients even if insurance coverage runs out. In this situation, the hospital could end up buying oral chemotherapy for some patients.

**Trends in Financing and Managing Oral Chemotherapy**

**Formulary Management:** The high cost of many new oral chemotherapies has set the stage for new management cost control strategies. Payers have limited ways of monitoring parenteral therapy; frequently the
therapy has already been administered when the payor receives an initial claim. However, oral therapy can be more tightly monitored and controlled through pharmacy benefits because the patient will present a prescription to a community or cancer center pharmacy or have the drug provided by specialty pharmacies contracted for by insurance companies.

One common strategy for pharmacy benefit management is the tiered drug formulary. Whether this strategy could be applied to oral chemotherapies is unclear, however, at least for the foreseeable future. For example, states have variable regulations regarding what drugs must be included in a formulary. Oncology drugs often must be included despite minimal data in the published literature, making it difficult to exclude even a few drugs.

Furthermore, formulary management is based on the preferential selection of one member from a class of drugs. Currently, no oral chemotherapy drug classes including multiple agents, making it impossible to apply formulary management. Additionally, head-to-head trials investigating the equivalence or potential superiority of 2 related drugs have not been done and are unlikely, because manufacturers have no financial incentive to do such studies. Sunitinib and sorafenib or cetuximab and panitumumab are examples of related agents; however, the differences among the multiple targets of these agents prevent them from being considered bioequivalent. The class of multikinase inhibitors that includes imatinib, nilotinib, sunitinib, dasatinib, sorafenib, and lapatinib is an example of a pharmacologic class that might lend itself to formulary management. In addition, gaps in the clinical data limit the ability to create a formulary system, be it simple or tiered.

Finally, the business premise of formularies is that the manufacturer will provide a pricing discount if their drug is favorably listed on the formulary. This may not apply to biologic therapies, however, because negotiating discounts are only possible when a different manufacturer makes 2 similar compounds for the same indication. Dasatinib and nilotinib are both tyrosine kinase inhibitors used to treat CML, and they are made by different manufacturers. However, a manufacturer will only be receptive to providing a discount if the payor can prove that usage of the drug will increase if it is preferentially placed on the formulary. This can be more difficult to prove for oral chemotherapy than for drugs in non-cancer therapeutic classes. In summary, the lack of a cogent argument for a managed care company to favor a particular agent or agents impairs the availability of market forces (e.g. discounts) to limit the costs of these compounds via the implementation of formularies for oral chemotherapy.

Preference for generic drugs is another basic formulary management strategy, but creating generic versions of bioengineered therapies will be very difficult. For example, for a pharmaceutical drug, generic manufacturers need only demonstrate that the generic has the same chemical formula and bioavailability. This cannot be done with bioengineered drugs, however, and regulators are considering whether generic versions of bioengineered therapies must reach the same standards of research and testing as their predecessor. The issue of FDA regulation of generic versions or “biosimilars” of bioengineered drugs has been a hotly debated issue for years.

Value-Based Co-Insurance: Value based co-insurance is essentially a form of health care rationing controlled by the patient in which incentives are put into place to promote the use of high-value interventions. This concept is similar to current pharmacy formularies, but applied on a broader scale to the comparative effectiveness of procedures, diagnostic services, and medical devices. In the context of oral chemotherapy, a drug that has been shown to have a very minimal incremental benefit on progression-free survival would have a high rate of co-insurance. In contrast, a drug such as imatinib, which may be considered curative or at least associated with a long progression-free survival, would have minimal co-insurance.

Objections to value-based plans include the inequity of a tiered benefit. However, other experts point out the inequity of the current situation of millions of uninsured Americans who lack access to essential health benefits. The values applied to different chemotherapy scenarios will obviously be controversial and will require additional data on clinical and comparative effectiveness.

Annual and Life Time Maximums for Cancer Care: Annual and lifetime maximum covered amounts are another strategy used by employers, particularly smaller ones, to limit their financial exposure with beneficiaries with serious or life-threatening illnesses. However, this type of coverage often creates an underinsured population of patients, especially in cancer care. Although coverage amounts may seem adequate to
average consumers, patient undergoing extensive treatments may find the inadequacy of these coverage maximums readily and tragically apparent.

**Conclusions**

Oral chemotherapy is emerging as an alternative for appropriately selected patients who, with support from

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Advantages and Disadvantages of Oral Compared With Parenteral Chemotherapies</th>
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<tbody>
<tr>
<td><strong>Patient</strong></td>
<td><strong>Physician/Health Care Team</strong></td>
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<tr>
<td><strong>Safety/Adherence</strong></td>
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<tr>
<td>Oral</td>
<td>Patients assume greater responsibility and control</td>
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<tr>
<td>Parenteral</td>
<td>Adherence based on controlled administration in clinic or office</td>
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<td><strong>Convenience</strong></td>
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<tr>
<td>Oral</td>
<td>Convenience gain only if oral chemotherapy is NOT given with parenteral therapy</td>
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<tr>
<td>Parenteral</td>
<td>Often has shorter duration of therapy than oral</td>
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<td><strong>Drug Supply and Distribution</strong></td>
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<tr>
<td>Oral</td>
<td>Can receive from hospital pharmacy, mail order, or specialty pharmacy</td>
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<tr>
<td>Parenteral</td>
<td>Requires office visit</td>
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<td><strong>Communication Issues</strong></td>
<td></td>
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<tr>
<td>Oral</td>
<td>Requires new patient education</td>
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<tr>
<td>Parenteral</td>
<td>Infusion sessions allow for prolonged contact of the patient with the health care team.</td>
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<td><strong>Oncology Infrastructure</strong></td>
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<tr>
<td>Oral</td>
<td>Potentially fewer office visits; follow up may occur at specialty monitoring clinics</td>
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<tr>
<td>Parenteral</td>
<td>Office set up specifically for parenteral therapy</td>
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<td><strong>Financing</strong></td>
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<tr>
<td>Oral</td>
<td>May face significant cost sharing, including Medicare Part D “donut hole”</td>
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<tr>
<td>Parenteral</td>
<td>May have better coverage compared with oral</td>
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their clinicians, can adequately manage the challenges. Some patients may respond to an increased sense of control associated with the self-management of some of their care, others may prefer to avoid the multiple office visits and intravenous infusions required in parenteral chemotherapy. Additionally, some oral chemotherapies may be associated with fewer side effects than parenteral alternatives. However, the promise of oral chemotherapies will only be realized with careful attention to the safety and monitoring requirements.

The growing number of oral chemotherapies, either currently marketed or in the development pipeline, will significantly impact all aspects of oncology care. From the oncologist’s perspective, oral chemotherapies may have a major impact on office practice, reducing the traditional revenues derived from the administration of parenteral therapy and requiring heightened attention to the selection of patients who are appropriate candidates for oral chemotherapy, with subsequent monitoring and support for adherence. The patient–physician relationship may be altered, with fewer oncology office visits and an increased need to coordinate cancer care with other entities, such as specialty pharmacies or clinics.

For older patients, the advent of Medicare Part D ensures that they will not be subject to catastrophic medical costs related to oral chemotherapy, but significant gaps in drug reimbursement still exist. In addition, in response to the growing cost of pharmaceuticals, employers are contemplating other benefit designs, such as lifetime caps on cancer care coverage, higher deductibles, co-pays, or co-insurance.

Oral chemotherapy has been conceptualized as a convenient, less toxic form of therapy that will be driven by patient preference. However, many of the safety issues related to oral chemotherapy are underappreciated, and many patients will not be appropriate candidates. Safety issues include the lack of checks and balances to avoid medication errors, possible lack of patient adherence, and a shift in the responsibility for managing a potentially complicated oral regimen to the patient. The risks and benefits of oral chemotherapy from the patient, physician and health care system perspective shown in Table 2. Clinicians should note that many of the disadvantages listed are not inherent to oral chemotherapy, but reflect the fact that adequate safety and support systems have not evolved as quickly as oral chemotherapy agents.

References
1. Which of the following drugs is/are available in an oral formulation?
   a. Imatinib
   b. Lapatinib
   c. Capecitabine
   d. Lenalidomide
   e. All of the above

2. Which of the following is/are considered drivers of oral chemotherapy?
   a. New oral biologic therapies are primarily cytostatic in nature and require daily therapy.
   b. Molecular monitoring of disease has prolonged duration of treatment, favoring oral therapy.
   c. The perception exists that patients clearly prefer oral therapy.
   d. Biologic agents have predictable absorption.
   e. Only a and c above
   f. Only a, b, and c above

3. Which of the following is/are TRUE about patient preference for oral therapy?
   a. Although oral monotherapy may avoid the inconvenience of an office visit, many combination therapies include parenteral therapy, and therefore require an office visit anyway.
   b. Most oral chemotherapy regimens are simple for the patient to manage.
   c. Oral chemotherapy will shift some aspects of managing chemotherapy to the patient; not all patients respond positively to this empowerment.
   d. Only a and c above
   e. a, b, and c above

4. Which of the following is/are common misperceptions about oral chemotherapy?
   a. Oral chemotherapy has fewer side effects than parenteral chemotherapy.
   b. Oral chemotherapy is particularly appropriate for frail elderly patients.
   c. Monitoring the side effects of oral chemotherapy is easier than monitoring the side effects of parenteral therapy.
   d. Only a and b above
   e. a, b, and c above

5. Which of the following is/are TRUE about adherence to oral chemotherapy?
   a. Adherence is an important factor that can NOT be easily assessed with a questionnaire.
   b. Adherence to oral chemotherapy in general is very good, as is illustrated by the excellent long-term adherence to imatinib therapy.
   c. Payor information systems that can capture whether or not the prescription is filled are in place and provide additional evidence of assurance.
   d. All of the above
   e. None of the above

6. Which of the following is/are accepted as reliable techniques for monitoring adherence?
   a. Directly ask the patient
   b. No completely reliable method of monitoring adherence is currently available.
   c. Patient diaries, pill counts
   d. Rates of prescription refills
   e. Only a and c above

7. Which of the following is/are TRUE about the steps that have been taken to ensure the safety of oral chemotherapy?
   a. The same level of checks and balances that are used for parenteral chemotherapy have been developed for oral chemotherapy, thus reducing the risk of medication errors.
   b. Standard order forms have been developed for oral chemotherapy.
   c. Oral chemotherapy prescriptions are routinely reviewed by 3 or 4 licensed health care staff.
   d. All of the above
   e. None of the above

8. What are the key communications issues regarding oral chemotherapy?
   a. Making every effort to obtain an accurate medication history from the patient, electronic medical record, payer information systems, or pharmacy records
   b. Ensuring adequate time to counsel patients
   c. Widespread use of online reporting systems for toxicities
   d. Only a and b above
   e. None of the above

9. Which of the following is/are FALSE about the impact of oral chemotherapy on oncology practice?
   a. The transition to oral chemotherapy will result in an overcapacity of infusion centers.
   b. The oncologist’s revenue and office structure is geared around the delivery of parenteral therapy and thus may decline.
   c. Financial incentives favoring parenteral therapy for both patients and physicians may influence treatment decisions.
   d. All of the above are false.
   e. None of the above are false.

10. What are the potential advantages of specialty pharmacies?
    a. The specialty pharmacist interacts directly with the patient, providing additional education and counseling.
b. Specialty pharmacies are more flexible in the number and dosages of pills provided with a single prescription.

c. Dedicated hot lines allow the specialty pharmacists to easily communicate with the prescribing physician.

d. Only a and b above

e. None of the above

11. What are the implications of the “donut hole” in Medicare Part D coverage?

a. The high cost of many oral chemotherapies ensures that many patients will experience a “donut hole” in Medicare coverage.

b. Patient assistant programs adequately address the “donut hole” for many patients.

c. When possible, patients may opt for parenteral therapy to avoid the “donut hole.”

d. Only a and c above

e. All of the above

12. Which of the following statement(s) about formulary management strategies for oral chemotherapy is/are TRUE?

a. State mandates have facilitated formularies for oral chemotherapy.

b. Several chemotherapy drug classes have multiple agents, thus limiting formulary management.

c. Head to head trials of oral chemotherapies can serve as the basis of formulary management.

d. Only a and c above

e. None of the above

Post-Test Answer Sheet

Please circle one answer per question. A score of at least 70% on the post-test is required.

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<th>Question</th>
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Please evaluate the achievement of the learning objectives using a scale of 1 to 5.

(1 = Not met; 3 = Partially met; 5 = Completely met)

Outline how oral chemotherapy is financed and how payment issues for oral chemotherapy may differ from those of parenteral chemotherapy

1 2 3 4 5

Recognize the common misperceptions about oral chemotherapy and discuss these with patients

1 2 3 4 5

Utilize patient selection criteria for oral chemotherapy regimens

1 2 3 4 5

Summarize the impact that widespread use of oral chemotherapies may have on oncology practice

1 2 3 4 5

Please indicate the extent to which you agree or disagree with the following statements:

(1 = Strongly disagree; 3 = Not sure; 5 = Strongly agree)

The material was presented in a fair and balanced manner.

1 2 3 4 5

The information presented in this monograph was pertinent to my educational needs.

1 2 3 4 5

The information presented was scientifically rigorous and up-to-date.

1 2 3 4 5

The information presented in this monograph has motivated me to modify my practice.

1 2 3 4 5

I would recommend this monograph to my colleagues.

1 2 3 4 5
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Expiration Date: March 31, 2009

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