REVIEW

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The promise of targeted therapy: Cancer drugs become more specific

ABSTRACT

Toxic chemotherapeutic agents are slowly being supplemented by a new generation of drugs that recognize specific targets in or on cancer cells. Although these molecular and genetic approaches are in their infancy, they hold the promise of more effective therapies with markedly fewer side effects. Several targeted agents are already approved by the US Food and Drug Administration (FDA) for use in malignancies, and numerous others are in clinical trials.

KEY POINTS

One approach is to design monoclonal antibodies that attach to tumor cells and either mark the cell for attack by the immune system, block specific receptors, or deliver antitumor agents. Several monoclonal antibodies are approved for treating malignancies.

Another approach is to inhibit signaling pathways for growth and proliferation within tumor cells. Imatinib (Gleevec), a small-molecule drug that blocks several intracellular signaling pathways, has become the standard of care in chronic myelogenous leukemia, and it shows promise for treating advanced gastrointestinal stromal tumors.

Gene therapy holds great promise for blocking expression of oncogenes or replacing missing or defective tumor-suppressor genes. A major obstacle remains the lack of efficient and selective vectors to deliver genes.

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This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

CANCER THERAPY is getting smarter, with new drugs that act specifically against cancer cells.[1] Eleven of these new "targeted" agents have been approved by the US Food and Drug Administration (FDA) in the past 5 years (**TABLE 1**), and more are in development.

The problem with traditional chemotherapy and radiation therapy is that they are indiscriminate: although they kill rapidly proliferating cells such as tumor cells, they also affect normal cells.

Traditional chemotherapy and radiation therapy won't disappear anytime soon, but more and more they will be supplemented by therapies that target tumor cells without affecting normal cells, eg:

- Monoclonal antibodies that attach to tumor cells and either mark the cell for attack by the immune system, block specific transmembrane receptors, or deliver chemotherapeutic or radioactive drugs
- Drugs that inhibit signaling pathways for growth and proliferation within tumor cells
- Therapy to block expression of oncogenes and even perhaps replace missing or defective tumor-suppressor genes—the specific abnormalities that triggered the normal cell to become neoplastic in the first place and that allow the tumor cell to proliferate indefinitely. Other aims of gene therapy are to make tumor cells more susceptible to standard chemotherapy or radiotherapy or to make normal tissues less susceptible to the damage induced by conventional treatments, allowing use of higher doses.

This field is still in its infancy. No single strategy appears to be the most successful as yet, and new strategies will likely emerge. In the following pages we discuss each of these approaches.

MONOCLONAL ANTIBODIES AGAINST CANCER CELLS

Some surface antigens are present predominantly or exclusively on malignant cells and not the surrounding normal cells. These tumor-associated antigens make excellent targets for specific antibodies to bind to.

When some of these antibodies bind to the tumor cell they can trigger a host immune reaction that leads to cell death. Others serve as transport vehicles, delivering attached radioisotopes, immunotoxins, or cytotoxins to tumor cells (FIGURE 1).

Several monoclonal antibodies have been approved, most of them for treating hematologic malignancies.

Rituximab

Rituximab (Rituxan) is a chimeric monoclonal antibody that binds to CD20, a cell-surface protein found almost exclusively on mature B cells, including those in B-cell non-Hodgkin lymphoma. It was approved in 1997, making it the first monoclonal antibody available in the United States for treating malignant disease.

Rituximab was the first monoclonal antibody approved for treating malignant disease in the US

Indications. Rituximab's original indication was for treating B-cell non-Hodgkin lymphoma (low-grade or follicular) that has relapsed and is refractory to treatment. It is currently being used either alone or in combination with standard chemotherapeutic regimens in a variety of malignant and nonmalignant B-cell disorders.

Efficacy. The pivotal clinical trial of rituximab included 166 patients with relapsed or unresponsive non-Hodgkin lymphoma. The tumors regressed for more than 3 months in 48% of the patients treated.[2]

Additional clinical trials found rituximab beneficial in other hematologic disorders, including intermediate-grade and high-grade non-Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma, Waldenström macroglobulinemia, hairy-cell leukemia, and autoimmune cytopenias.[3–9]

Side effects. Most patients tolerate rituximab well; the most common side effects are fever, chills, and nausea. Less frequent toxicities include hypotension, bronchospasm, and neutropenia.

Gemtuzumab

Gemtuzumab (Myelotarg) is composed of a recombinant humanized monoclonal antibody linked to a molecule of calicheamicin, a cytotoxic antitumor antibiotic. It is the first such targeted antibody-chemotherapy complex available.

The antibody binds specifically to CD33, an antigen found on normal and leukemic myeloid cells, including 90% of acute myeloid leukemia blasts. CD33 is not present on bone marrow stem cells, which therefore are not affected by the treatment and regenerate normal myeloid cells after therapy.

Indications. Gemtuzumab is approved for patients older than 60 years with CD33-positive acute myeloid leukemia (AML) who have relapsed after initial treatment and are not considered candidates for cytotoxic chemotherapy.

(Approximately 75% of patients with acute myeloid leukemia who achieve a first remission have a relapse, and the prognosis is dismal in patients who are not candidates for stem cell transplantation. Although a number of chemotherapy regimens are used in this situation, there is no standard of care.)

Efficacy. Three studies were conducted in a total of a 142 patients who had acute myeloid leukemia in first relapse.[10] The disease responded for more than 6 months in 30% of patients who received gemtuzumab monotherapy.

Phase 2 studies show promising results when gemtuzumab is used in combination with standard chemotherapy in the treatment of newly diagnosed acute myeloid leukemia.

Side effects are similar to those of chemotherapy, and include myelosuppression, hypersensitivity reactions, pulmonary toxicity, hepatotoxicity (increased liver enzymes), and veno-occlusive disease. Owing to the calicheamicin moiety, this drug has more substantial side effects than other targeted agents.

Alemtuzumab

Alemtuzumab (Campath) is a humanized monoclonal antibody that binds to CD52, an antigen expressed on B and T lymphocytes.

Indications. Alemtuzumab is approved for patients with B-cell chronic lymphocytic leukemia for whom other therapy has failed.

TABLE 1

Approved targeted drugs

Alemtuzumab (Campath)
- **Mechanism:** Humanized monoclonal antibody against CD52 antigen (expressed on lymphocytes)
- **Indications:** B-cell chronic lymphocytic leukemia in patients for whom alkylating agents have failed
- **Toxicities:** Myelosuppression

Bevacizumab (Avastin)
- **Mechanism:** Humanized monoclonal antibody against vascular endothelial growth factor (VEGF)
- **Indications:** First-line treatment for metastatic colorectal cancer
- **Toxicities:** Hypertension, intestinal perforation (rare)

Bortezomib (Velcade)
- **Mechanism:** Proteasome inhibitor
- **Indications:** Multiple myeloma relapsed after two prior treatments
- **Toxicities:** Gastrointestinal symptoms, fatigue, thrombocytopenia, and sensory neuropathy

Cetuximab (Erbitux)
- **Mechanism:** Chimeric monoclonal antibody against epidermal growth factor receptor (EGFR)
- **Indications:** EGFR-positive, irinotecan-refractory metastatic colorectal carcinoma
- **Toxicities:** Acneiform rash, folliculitis, hypersensitivity reactions

Gefitinib (Iressa)
- **Mechanism:** Tyrosine kinase inhibitor
- **Indications:** Third-line treatment of non-small cell lung cancer
- **Toxicities:** Diarrhea, nausea, rash, pulmonary toxicity

Gemtuzumab (Myelotarg)
- **Mechanism:** Cytotoxic antibiotic calicheamicin linked to a humanized monoclonal antibody against CD33 antigen (expressed on myeloid cells)
- **Indications:** CD33-positive acute myeloid leukemia in patients older than 60 years who are not candidates for cytotoxic therapy
- **Toxicities:** Myelosuppression

Ibritumomab tiuxetan (Zevalin)
- **Mechanism:** Radioisotope yttrium linked to a murine monoclonal antibody against CD20 antigen (expressed on mature B cells)
- **Indications:** Low-grade and follicular B-cell non-Hodgkin lymphoma refractory to rituximab
- **Toxicities:** Neutropenia, thrombocytopenia

Imatinib (Gleevec)
- **Mechanism:** Inhibitor of Bcr-Abl and c-kit tyrosine kinases
- **Indications:** Chronic myelogenous leukemia and gastrointestinal stromal tumors
- **Toxicities:** Nausea, diarrhea, myalgia, edema

Rituximab (Rituxan)
- **Mechanism:** Chimeric monoclonal antibody against CD20 antigen (expressed on mature B cells)
- **Indications:** Refractory low-grade and follicular B-cell non-Hodgkin lymphoma
- **Toxicities:** Infusion-related symptoms: fever, chills, nausea, urticaria

Tositumomab (Bexxar)
- **Mechanism:** Radioisotope iodine 131 linked to a chimeric monoclonal antibody against CD20 antigen
- **Indications:** Follicular non-Hodgkin lymphoma, with or without transformation, that has relapsed after chemotherapy and is refractory to rituximab
- **Toxicities:** Myelosuppression

Trastuzumab (Herceptin)
- **Mechanism:** Humanized monoclonal antibody against HER2
- **Indications:** Metastatic breast cancer expressing HER2
- **Toxicities:** Cardiotoxicity

Generally, initial therapy for these patients includes chemotherapy such as chlorambucil and fludarabine.

Efficacy. The pivotal clinical trial with alemtuzumab included 93 patients with relapsed or refractory B-cell chronic lymphocytic leukemia. This population has a very poor prognosis, and only 40% survive for more than 1 year. The response rate was 33%, and the duration of response was more than 9.5 months.[11]

In subsequent trials, alemtuzumab was given to untreated patients with B-cell chronic lymphocytic leukemia, and response rates of up to 90% were reported. The response rates appear even higher when alemtuzumab is used in combination with fludarabine, the standard drug for chronic lymphocytic leukemia.

Promising clinical activity has also been reported in patients with T-cell malignancies such as mycosis fungoides and the Sézary syndrome, with healing of skin lesions and reduced itching.[12]

Side effects. The most common side effects include infections, viral reactivation, and myelosuppression.

The goal: stop the cancer but not harm normal cells

Ibritumomab tiuxetan

Ibritumomab tiuxetan (Zevalin) consists of two parts: ibritumomab, a murine anti-CD20 antibody that targets mature B cells; and tiuxetan, a linker-chelator that provides a high-affinity chelation site for the radioisotope yttrium-90.[13] It is the first radioconjugate targeted agent approved for treatment of cancer.

Indications. Ibritumomab is used for treating relapsed or refractory low-grade and follicular B-cell non-Hodgkin lymphoma, including rituximab-refractory follicular non-Hodgkin lymphoma.

(Although patients with low-grade non-Hodgkin lymphoma may remain in remission for years, they eventually relapse, with diminishing response to standard treatments over the course of the disease.)

Efficacy. Ibritumomab was approved on the basis of a phase 3 clinical trial that compared it with rituximab in 143 patients with refractory or relapsed, low-grade and follicular non-Hodgkin lymphoma.[14] Patients receiving ibritumomab were first treated with rituximab to clear peripheral B cells and improve the biodistribution of ibritumomab. Eighty percent of patients responded, compared with 56% treated with rituximab alone.

Side effects. Neutropenia and thrombocytopenia are the most frequent and serious side effects, occurring in more than 50% of patients. Other toxicities include nausea, vomiting, and anorexia.

Tositumomab

Tositumomab (Bexxar) is also a radioconjugate consisting of the anti-CD20 antibody tositumomab and radioactive iodine 131.

Indications. Tositumomab is approved for follicular non-Hodgkin lymphoma, with and without transformation, that has relapsed after chemotherapy and is refractory to rituximab.

Efficacy. Responses were achieved in 57% to 71% of patients in phase 1 to phase 3 trials. Tositumomab was shown to be effective in the subset of patients with transformed low-grade non-Hodgkin lymphoma, which is particularly resistant to conventional therapies. The durations of responses were significantly longer compared with the last remissions induced by chemotherapy.

Side effects. Hematologic toxicity is the major dose-limiting toxicity.

Bevacizumab

Bevacizumab (Avastin), a recombinant humanized monoclonal antibody, targets vascular endothelial growth factor (VEGF), which stimulates new vessel formation within the tumor.

Indications. Bevacizumab was recently approved as a first-line treatment for metastatic colorectal cancer.

Efficacy. When given in combination with irinotecan, 5-fluorouracil, and leucovorin (one of the standard regimens for colon cancer), bevacizumab prolonged survival by about 5 months.[15] This is the first antiangiogenic agent that has been shown to induce an increase in overall survival.

Side effects. A moderate increase in hypertension was noted in patients receiving bevacizumab. A rare but serious side effect was the occurrence of intestinal perforation.

Targeted cancer therapy

A new generation of cancer drugs draws upon discoveries in molecular biology to kill or inhibit cancer cells while not affecting normal cells.

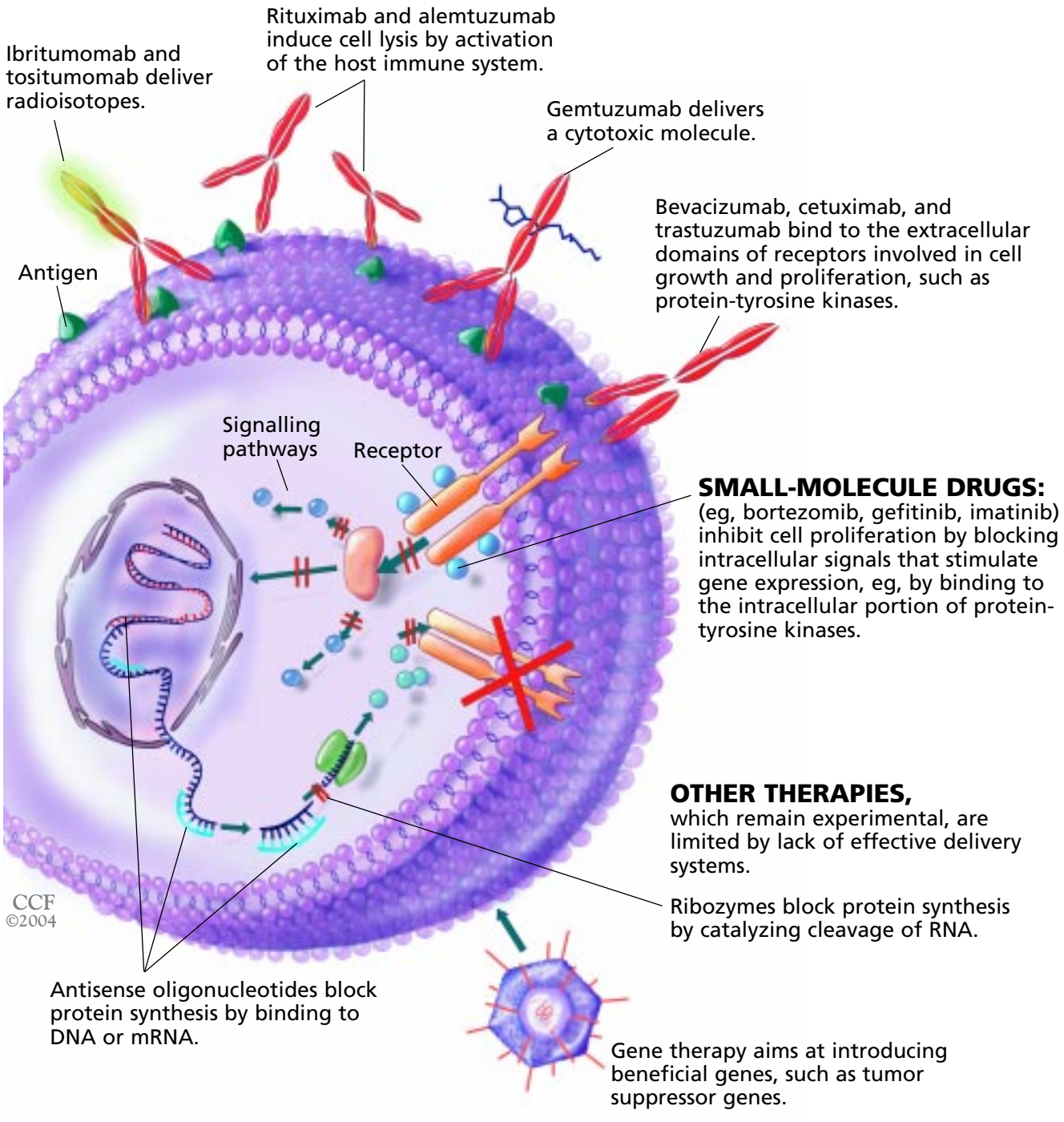

FIGURE 1

Cetuximab

Cetuximab (Erbitux) is a chimeric monoclonal antibody that binds the epidermal growth factor receptor (EGFR) in its extra-cellular domain. In preclinical studies activity was demonstrated in a wide range of human cancer cell lines.

Indications. Cetuximab was recently approved for treatment of EGFR-positive, irinotecan-refractory colorectal carcinoma.

Efficacy. In a randomized study comparing the combination of cetuximab and irinotecan with cetuximab as a single agent in patients with EGFR-expressing, irinotecan-refractory colorectal carcinoma,[16] the objective response rate for the combination was 23% compared with 11% for the single agent. The response rate was significantly higher among patients who experienced skin rash.

Side effects. Acneiform rash and folliculitis involving the face and upper chest occurred in 80% of patients. Hypersensitivity reactions have been reported.

AGENTS THAT CONTROL PROLIFERATION

Malignant cells can proliferate indefinitely and have lost the normal signals that tell them to undergo apoptosis

The main difference between malignant and normal cells is that malignant cells can proliferate indefinitely and have lost the normal signals that tell them to undergo apoptosis, ie, die.

Normal cell growth and replication is a very complicated and organized process. DNA contains the code for the synthesis of various proteins, including growth factors that bind to surface receptors of the same cell or cells of the surrounding or distant tissues. This binding activates signaling pathways within the cell that relay information back to the nucleus and activate mechanisms responsible for cell division and proliferation.

Abnormalities along these pathways can lead to malignant transformation and uncontrolled cell proliferation. These abnormalities can, however, be targeted to inhibit cell proliferation, induce apoptosis, or both.

The problem with this approach is that very few malignancies are due to a single abnormality, and in fact most cancer cells sustain several mutations before turning malignant. This makes most malignancies in individual patients unique—even tumors in the same location and of the same histopathologic type will differ between patients. Therefore, one approach does not fit all.

Nevertheless, some of the most encouraging results have been achieved with drugs such as imatinib and trastuzumab, which target single abnormalities (see below).

Surface receptors are prime targets

Most surface receptors that are aberrant in malignancies are enzyme-linked; an exception are the G protein-linked receptors, which have a role in the pathogenesis of certain endocrine tumors.

There are four classes of enzyme-linked receptors: guanylyl cyclases, tyrosine phosphatases, serine/threonin kinases, and protein-tyrosine kinases. The latter three play an important role in malignant transformation.

Protein-tyrosine kinases

Protein-tyrosine kinases are transmembrane or cytosolic enzymes that transfer a phosphate group from adenosine triphosphate to specific amino acids in proteins after a factor such as epidermal growth factor binds to its receptor. This leads to the activation of signaling pathways. Included in this process are many growth factors, differentiation factors, and hormones, many of which have been implicated in cell growth, differentiation, proliferation, and death. This process can also be involved in tumor progression and metastasis.

So far, more than 100 protein-tyrosine kinases have been identified, including epidermal growth factor receptor, platelet-derived growth factor receptor, vascular endothelial growth factor receptor, and cytosolic Abelson (Abl) tyrosine kinase.

Epidermal growth factor receptors have an established role in carcinogenesis and tumor growth, and they are prime targets for therapy. There are four types of epidermal growth factor receptors: ErbB-1 (HER1), ErbB-2 (HER2, HER2/neu), ErbB-3 (HER3), and ErbB-4 (HER4).

These receptors bind a wide variety of ligands, and are present on many solid epithelial tumors, including cancers of the head and neck, lung, colon, breast, and kidney. This expression may be associated with early metastasis and poor outcome.[17]

Blocking protein-tyrosine kinases

Drugs that inhibit cell surface receptors have shown promising clinical results. Two types of agents are used to block or inhibit the protein-tyrosine kinases:

- Monoclonal antibodies, which inhibit the intramembranous part of the receptor, and
- Small-molecule drugs (molecular weight < 600 daltons), which inhibit the intracellular portion.

Three protein-tyrosine kinase inhibitors have been approved: trastuzumab, imatinib, and gefitinib; several others (eg, erlotinib, ABX-EGF) are in preclinical and clinical development.

Trastuzumab

Trastuzumab (Herceptin), a humanized monoclonal antibody, inhibits cell growth by binding to the extracellular part of the HER2 protein-tyrosine kinase receptor, which is involved in the pathogenesis of breast and ovarian cancer. Trastuzumab induces antibody-dependent cellular toxicity by natural killer cells and monocytes against malignant cells.

Indications. Trastuzumab is used alone or in combination with paclitaxel for treating breast cancer that is refractory to standard chemotherapy. Patients must have cancer cells with high levels of HER2 (present in 25%–30% of breast cancers and associated with a more aggressive form of malignancy). HER2 overexpression is also found in other solid tumors including ovarian, prostate, and non-small cell lung cancer.

Efficacy. The tumor regression rate in patients with metastatic breast cancer overexpressing the HER2 protein treated with trastuzumab is 26%.[18] This is comparable to many single-agent chemotherapies used as second-line or third-line treatments.

A phase 3 clinical trial in 469 patients with metastatic breast cancer, all overexpressing HER2, compared standard chemotherapy (anthracycline plus cyclophosphamide or paclitaxel) vs trastuzumab plus chemotherapy.[19] The response rate in the combination therapy group was 50%, vs only 32% with chemotherapy alone. The median survival time was 25 months for patients receiving combination therapy vs 20 months for the chemotherapy-alone group. These data illustrate the potential enhancement of chemotherapy by the addition of trastuzumab.

The role of trastuzumab as adjuvant therapy following curative surgery for early breast cancer is being explored. In addition, trastuzumab combined with chemotherapy has been studied in patients with non-small cell lung cancer and prostate cancer whose tumors express the HER2 receptor. No significant benefit was found in those studies.[20,21]

Side effects. The most important adverse reaction was cardiac dysfunction, which occurred in 27% of patients in the combination therapy group compared with 8% in patients receiving chemotherapy alone. The incidence of cardiac dysfunction was highly dependent on prior anthracycline exposure.

Further studies showed that the ErbB-2 (HER2) receptor, together with its coreceptor ErbB-4 and the ligand neuregulin-1, are essential for normal development of heart muscle.[22] The incidence of cardiac dysfunction with trastuzumab as monotherapy is, however, only 1%.

Trastuzumab is otherwise well tolerated. The most common side effects are mild to moderate infusion-associated symptoms, myelosuppression, and diarrhea.

Most malignancies in individual patients are unique

Imatinib

Imatinib (Gleevec), a small-molecule drug, inhibits the intracellular part of three protein-tyrosine kinases:

- Bcr-Abl, an abnormal fusion protein involved in the pathogenesis of chronic myelogenous leukemia. It is a product of the Philadelphia chromosome, a genetic abnormality present in patients with chronic myelogenous leukemia.
- c-kit (CD117), a receptor overexpressed in gastrointestinal stromal tumors[23]
- Platelet-derived growth factor receptor alpha (involved in chronic myeloproliferative syndromes characterized by eosinophilia).

Since the drug has a very low molecular weight, it can be given orally.

Efficacy. Imatinib has become the standard of care in chronic myelogenous leukemia, and it shows efficacy for treating advanced gas-

trointestinal stromal tumors.

Clinical trials with this drug included more than 700 patients with chronic and advanced chronic myelogenous leukemia.[24,25] Leukocyte and platelet counts normalized in more than 80% of patients. The genetic abnormality characteristic of chronic myelogenous leukemia was also affected: the Philadelphia chromosome decreased or disappeared in 40% of treated patients as the malignant cells with this abnormality were eliminated with treatment. This is undoubtedly the most successful example of targeted therapy.

A multicenter phase 2 trial evaluated imatinib in treating gastrointestinal stromal tumors, which arise from stromal tissue anywhere along the gastrointestinal tract, most often the stomach. Until recently, the only effective treatment was total surgical resection, since this tumor is resistant to conventional chemotherapy and radiation. Once metastatic, it was invariably fatal.

The study included 147 patients with unresectable or metastatic gastrointestinal stromal tumors that expressed CD117.[26] The tumors shrank in 54% of treated patients and remained stable in 28%.

Side effects. Imatinib is well tolerated, and adverse effects are minimal. These include nausea, myalgia, edema, and diarrhea.

A major obstacle to gene therapy is the lack of efficient vectors to deliver genes

Gefitinib

Gefitinib (Iressa), a small-molecule drug, inhibits the intracellular portion of the receptor HER1, which is involved in the pathogenesis of several types of cancer. It is orally active.

Indications. Gefitinib was approved by the FDA in May 2003 as a third-line treatment for non-small cell lung cancer.

Efficacy. The approval was based on two nonrandomized studies,[27,28] in which more than 400 patients with previously treated lung cancer—a very refractory type of tumor—received gefitinib alone. Tumors regressed in 10% of treated patients.

Randomized studies of gefitinib in combination with chemotherapy in lung cancer patients have not shown any statistically significant benefit in survival, response rate, or time to progression, however. The reasons for this are unclear. A recent study[29] showed that specific mutations in the EGFR gene correlate with clinical responsiveness to gefitinib.

Side effects are mild, and included diarrhea, nausea, acne-like rashes, and pulmonary toxicity.

Many critics argued against the approval of gefitinib, since more than 200 of 29,000 patients who received it in Japan, where it was previously approved, died of side effects. Most deaths were due to acute pulmonary toxicity, including acute respiratory distress syndrome and pneumonia.

Blocking intracellular signaling pathways

Signaling pathways within malignant cells can also be inhibited. One enzyme that has been targeted is farnesyltransferase, which activates the Ras protein, a proto-oncogene involved in growth factor signaling. Ras is overexpressed in a variety of solid tumors and hematologic malignancies.

Small molecules that inhibit farnesyltransferase appear to have activity in various malignancies and have acceptable toxicity. These drugs remain experimental.

Proteasome inhibitors

A recently explored target present in all cells is a multienzyme complex called proteasome. The function of proteasome that is exploited in experimental therapy is degradation of proteins that regulate cell cycle progression. One such agent, bortezomib, was recently approved by the FDA.

Bortezomib

Bortezomib (Velcade) is a small molecule that induces selective inhibition of the proteasome in multiple myeloma cells.

Indications. Bortezomib is indicated for patients with multiple myeloma that has relapsed after two prior treatments and has demonstrated resistance to the last treatment received.

Efficacy. In a study of 202 patients who had received at least two prior therapies and demonstrated disease progression on their most recent therapy, 23% showed a response. The response lasted a median of 1 year.[30]

Side effects. The most common were gastrointestinal symptoms, fatigue, thrombocytopenia, and sensory neuropathy.

TARGETING GENETIC ABNORMALITIES

Many genes have oncogenic potential; these are categorized as either tumor-suppressor genes or oncogenes.

Replacing defective or absent tumor-suppressor genes

Tumor-suppressor genes normally keep cell replication in control, and if they are absent or their function is decreased, cells can turn malignant. An example is the p53 gene, which is mutated in many malignancies or absent in certain inherited cancers.

Mutant or missing tumor-suppressor genes can be replaced in vivo. Since current gene-transfer techniques do not efficiently deliver genes to all tumor cells, attempts have been made to inject genes locally, such as in head and neck cancers. In these instances, effects were observed, but the overall results were not encouraging.

Blocking oncogenes

Oncogenes can induce malignant transformation if their functioning is increased. Mutated or overexpressed oncogenes can be inactivated or down-regulated using antisense oligonucleotides or ribozymes.

Antisense oligonucleotides are short pieces of synthetic DNA or RNA. They can block gene expression by binding to their complementary strands of DNA or RNA. The most common target is messenger RNA. Binding to messenger RNA cleaves it and inhibits the synthesis of the protein in question.

These agents, however, have limited utility. They fall apart rapidly in tissues and penetrate cells poorly because they are ionic. Chemical alterations and synthetic carriers are being investigated to overcome these difficulties. Nevertheless, antisense oligonucleotides remain experimental, and no definite clinical benefits have been demonstrated to date.

Ribozymes are enzymes that catalyze the cleavage of RNA. They can be used therapeutically to cleave RNAs such as the Bcr-Abl transcript involved in chronic myelogenous leukemia. The problems with these agents also include inadequate delivery to the target malignant cells.

Other uses for gene therapy

Another use for gene therapy is to modify genetic information to make tumor cells more susceptible to cytotoxicity or to make normal tissues less susceptible to damage by chemotherapy. The strategies include immunomodulation via vaccination of cytokine gene-transfected tumor cells, suicide gene therapy, and chemoprotection.

Immunomodulatory gene therapy. About half of clinical trials of gene therapy have been designed to augment the immune response of patients against their cancer.

Immunomodulatory gene therapy has used irradiated tumor cells obtained from the patient's tumor and transduced in vitro with cytokine genes, such as those for interleukin 2 or granulocyte-macrophage colony-stimulating factor. The tumor cells then produce the immunoregulatory cytokine or initiate a cellular immune response and tumor rejection.

Another approach is immunization with genes that encode tumor antigens either directly or by transfer of antigen-presenting cells containing genes for tumor-associated antigens. Tumor tissue containing tumor-specific antigens is obtained from the patient, exposed in vitro to antigen-presenting dendritic cells obtained by processing the patient's monocytes, and subsequently injected back into the patient. This leads to stimulation of tumor-specific cytotoxic T lymphocytes, thought to be a crucial part of the immune response against tumors.

Genes can be replaced, but results have not been encouraging

This approach can be used to treat residual tumor tissue or to prevent tumor recurrence in patients at high risk.

Suicide gene therapy uses viral vectors that preferentially infect dividing cells, eg, tumor cells. The viruses are engineered to carry a gene for an enzyme that converts a nontoxic chemotherapy prodrug into its active metabolite. When the virus infects the tumor cell, it introduces the gene into the tumor cell's DNA. Then, when the patient subsequently receives chemotherapy, the concentration of the active metabolite is highest in the tumor itself, where it produces more-targeted cytotoxicity.

Chemoprotection. Before a patient undergoes chemotherapy, bone marrow cells can be harvested and transduced in vitro with genes that confer drug resistance (eg, the multidrug

resistance gene) and then given back to the patient. In theory, higher chemotherapy doses can be given without lethal damage to bone marrow stem cells, increasing the probability of remission.

These approaches are being explored in clinical trials.

Obstacles and limitations

Gene therapy still has many limitations, and more research is needed to identify potential genetic targets and tumor-associated antigens.

A major obstacle remains the lack of efficient and selective vectors to deliver genes.[29] Viruses have been used for this purpose, but because an immunologic response occurs against the virus, they are not ideal agents. Gene therapy remains investigational as a targeted approach to cancer treatment.

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