

# Designer Drugs: New Directed Therapies for Cancer

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## Abstract

The last thirty years have witnessed major improvements in the survival of pediatric cancer patients. This has been due to improvements in the various modalities of cancer therapy as well as improvements in supportive care. Historically, cancer treatments have been developed in an empiric fashion and amplified to the limits of tolerance. As more is learned about the biology of oncogenesis, we hope it will become possible to design therapies to deal with the unique mechanisms involved in the development of specific types of cancer. These rational approaches to cancer therapy should improve efficacy and diminish the risks of toxicity. The era of “designer drugs” is just beginning with the introduction of therapeutic monoclonal antibodies against tumor antigens, and new small molecules that target specific tumors, such as retinoids and imatinib mesylate. This presentation will review these advances and provide a perspective on potential future directions in this field.

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The last thirty years have witnessed major improvements in the outcomes of treatment for cancer. These results have been due to advances in chemotherapy, including the maximization of dosage and the use of combinations of agents with different modes of action and toxicity. In addition, advances in supportive care, including improved blood products and more effective antibiotics have made it possible to successfully manage patients during extended periods of myelosuppression.

Until recently, the development of chemotherapeutic agents was largely empiric. Candidate drugs were tested for their ability to kill tumor cells in tissue culture and promising agents were given to animals, and then to patients, to assess toxicity and tolerance for increasing doses. Only then, were these agents tested for clinical efficacy in phase II trials, usually conducted in patients with end-stage, refractory disease. It is hardly surprising that relatively few new drugs have been developed.

Most chemotherapeutic drugs and radiation direct their effect on DNA, a component of normal and malignant cells. The relative selection of malignant cells for damage by these treatments (compared to normal cells) is not well understood and toxicity is often severe.

As we learn more about the nature of oncogenesis

and the biologic characteristic of malignant cells, it is becoming possible to focus drug development on the features of specific cancers with a view toward providing more rational therapy treatments that will specifically attack malignant cells and spare the normal cells. This will improve efficacy and diminish toxicity. This review will describe recent advances in cancer therapy using monoclonal antibodies and small molecules that have been successfully used in targeted therapy.

## 1. Monoclonal Antibody Therapy

The development of monoclonal antibodies has presented an opportunity to create molecules that recognize the unique markers that characterize cancer cells. In order for monoclonal antibodies to be useful therapeutic agents, the antigen toward which the antibody is directed must be present on most or all tumor cells, but not on crucial normal cells. The antibody must either directly kill, adhere to, or be internalized into the target cell.

One example of a useful monoclonal antibody is rituximab, a chimeric murine/human antibody against the CD20 determinant on B lymphocytes. This agent is ca-

pable of initiating complement-mediated cell lysis and antibody dependent cellular cytotoxicity, as well as inducing apoptosis of target cells. Numerous studies have documented activity of rituximab in large cell lymphoma, mantle cell lymphoma, and post-transplant lymphoproliferative disease, even in patients who have relapsed after extensive prior therapy. Furthermore, there is substantial response to repeat therapy with rituximab, in patients who relapse after a previous course of the agent.

The immediate side effects of rituximab are due to presumed cytokine release (fever, chills, myalgias, etc.) and tumor lysis syndrome. The latter may be particularly severe in patients with a high tumor burden at the time of initiating therapy. Hematopoietic suppression and its sequelae, bleeding and sepsis, are not major immediate problems, although prolonged suppression of antibody production is seen. This may be managed with supportive immunoglobulin therapy.

The lack of major or dose-limiting toxicity makes rituximab an attractive agent for use in patients whose general condition is fragile due to age or other debilitating diseases. This feature also offers the possibility of combining rituximab with standard chemotherapy, and trials are in progress to assess the additive efficacy of such combinations.

Some monoclonal antibodies to tumor cell determinants may not mediate tumor killing directly. Still, they may have therapeutic efficacy when used as transporters of cytotoxic molecules, such as radionuclides or toxins.

One such agent is gemtuzimab ozogamicin (Mylotarg). This monoclonal antibody is directed against CD33, a determinant present on most leukemic blasts in patients with acute myelogenous leukemia (AML). The mere binding of the antibody to the cell surface does not damage the cell, and therapeutic benefit of treatment with unconjugated antibody has not been shown.

When conjugated with calicheamicin, humanized anti-CD33 (Mylotarg) has efficacy in the treatment of AML. The conjugate binds to the cell surface at the CD33 site and after the CD33 sites are saturated, the complex is internalized. Subsequent to internalization, the proteolytic enzymes of the cell liberate the toxin, which damages DNA and results in apoptosis. The major side effect of Mylotarg is prolonged myelosuppression. The ideal patient candidates for this agent are fragile patients and those patients who are clearly headed toward hematopoietic stem cell transplantation.

Radioimmunoconjugates are another variation on this theme. At the Fred Hutchinson Cancer Research Center, a radioiodinated ( $I^{131}$ ) conjugate with a humanized anti-CD45 has been developed. It complexes with the CD45 antigen, which is present on all leukocytes. It becomes fixed in sites of leukocyte production, but since it is not internalized, the isotope is not cleaved or released to the whole body. Agents such as this may be particularly useful in delivering increased doses of radiation to a diffuse target organ (e.g., bone marrow) to augment tumor kill in preparation for hematopoietic stem cell transplantation.

## 2. Small Molecules

Numerous tumors are characterized by illegitimate chromosomal translocations which result in novel chimeric proteins. One such translocation, t(9:22), results in production of the BCR-ABL fusion protein that is the hallmark of chronic myelogenous leukemia (CML). The fundamental importance of this tyrosine kinase in the pathogenesis of CML has been well documented. Inhibition of the tyrosine kinase has been a therapeutic goal for CML.

One compound, a signal transduction inhibitor (STI 571), Imatinib mesylate (Gleevec), inhibits phosphorylation by the BCR-ABL tyrosine kinase, and thereby prevents the further consequences of the signal cascade. *In vitro*, Gleevec inhibits cellular proliferation of CML (and Ph<sup>1+</sup> ALL) cells in tissue culture. Clinical trials have demonstrated extraordinary activity in CML with virtually no toxicity at doses that produce maximal efficacy. Imatinib mesylate has activity in Ph<sup>1+</sup> ALL, as well as in gastrointestinal stromal tumors (GIST), a cancer which is characterized by a constitutively active related tyrosine kinase, c-Kit.

The duration of activity of Imatinib mesylate in patients with CML is not known. It is not clear whether, or when, this therapy may be discontinued. It is certainly less toxic than the therapeutic alternatives (interferon- $\alpha$  and stem cell transplantation), but only time will tell whether it will replace stem cell transplantation as treatment for those patients who are young and who have a histocompatible donor.

The use of all-trans-retinoic acid (ATRA) in patients with acute promyelocytic leukemia (APL) is another example of targeting the molecular basis of malignancy. Most patients with APL carry a translocation, t(15:17), which apposes the PML gene and the retinoic acid receptor alpha (RAR- $\alpha$ ) gene. In normal myeloid cells, retinoic acid activates histone deacetylase and a process of myeloid differentiation ensues. In cells with the 15;17 translocation, cells are unresponsive to physiologic doses of retinoic acid, but differentiate when exposed to pharmacologic doses of retinoic acid. ATRA can induce remissions successfully in most patients with APL without causing the coagulopathy that characterizes the response of APL to intensive standard chemotherapy. By combining the use of ATRA with standard chemotherapy, the outcome of treatment of APL has improved dramatically.

The molecular specificity of ATRA therapy is demonstrated by its lack of efficacy in a minority of patients with APL whose cells carry an alternative translocation. While the alternate gene rearrangement also involves the RAR- $\alpha$  gene, the other component does not allow the action of pharmacologic doses of ATRA.

## 3. Conclusions

We are entering a new era of cancer therapy. Improved understanding of the molecular origins of cancer

will provide novel opportunities to interfere with specific oncogenic processes and improve the efficacy of treatments with diminished toxicity.

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