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Biological Approaches to Cancer Therapy

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A. Introduction

Progress had been made over the past 5 years toward the development of specific biological approaches to the treatment of cancer. The techniques of genetic engineering and mass cell culture, and improved techniques in protein and nucleic acid sequencing have made available biologics as highly purified molecules. The most definitive investigations have been carried out with natural and cloned interferon-α preparations, and it is clear that the latter are capable of inducing responses primarily in patients with certain types of lymphomas and leukemias. Preliminary trials with murine monoclonal antibodies have demonstrated excellent in vivo tumor localization and transient clinical responses, but durable responses are rare events. Antibodies conjugated to drugs, toxins, and isotopes have greater antitumor activity in vitro and in animal models; clinical trials are currently under way.

B. Monoclonal Antibodies

Clinical trials with monoclonal antibodies in humans have been designed to approach preliminary questions with respect to the feasibility and toxicity of monoclonal antibody therapy and to the rationale for the use of these reagents. While most of these trials have involved single patients or small series of patients, early indications are that an unlabeled monoclonal antibody alone may have some therapeutic effect, albeit rather limited.

Results of serotherapy trials in patients with a wide variety of hematologic malignancies and solid tumors are shown in Table 1 [1–18]. Transient reductions (24–48 h) in circulating leukemia cells were common, as were transient improvements in cutaneous lesions in patients with cutaneous T-cell lymphoma. At least 50% of patients with B-cell lymphomas/leukemias treated with anti-idiotype monoclonal antibodies had partial responses; one patient had a complete response (lasting over 4 years). Excellent targeting of antibody to tumor cells was reported in most of these studies.

Sears and coworkers [15, 16] treated 20 patients with gastrointestinal tumors with the 17-1A IgG_{2a} antibody, 3 of whom remained tumor-free 22, 13, and 10 months after therapy. Houghton and coworkers [18] reported 3 partial responses in 12 patients with melanoma treated with an IgG_3 antibody recognizing a ganglioside antigen (G_{D3}). Interestingly, this antibody is cytotoxic in vitro with human complement and human effector cells. Inflammatory reactions were observed around tumor sites in some of the patients treated with this antibody.

Toxicities associated with monoclonal antibody therapy are generally quite mild. Fevers, chills, and urticaria are quite common but are not treatment-limiting toxicities. Rare patients have developed shortness of breath associated with the rapid infusion

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Table 1. *Monoclonal antibody clinical trials*

Disease	Antibody/class	Specificity	No. of patients	Toxicity	Effect	Institution	Reference
B-lymphoma	Ab89/IgG_{2a}	Lymphomas	1	Renal (transient)	Transient reduction in circulating cells	Dana-Farber	[1]
B-lymphoma	4D6/IgG_{2b}	Idiotype	1	None	Complete remission	Stanford	[2]
B-lymphoma	Anti-idiotype/ IgG_1 of IgG_{2a} or IgG_{2b}	Idiotype	10	Fever, chills, nausea, vomiting, headache, diarrhea, transient dyspnea	5 objective responses	Stanford	[3]
B-CLL	Anti-idiotype/ IgG_{2b} and IgG_1	Idiotype	1	Fever, urticaria	Transient reduction in circulating cells	NCI	[4]
B-CLL	T101/IgG_{2a}	T65	13	Dyspnea, hypotension, fever (101–102° F), urticaria	Transient reduction in circulating cells	NCI	[5]
B-CLL	T101/IgG_{2a}	T65	4	Dyspnea, hypotension, fever, malaise, urticaria	Transient reduction in circulating cells	U. Calif. San Diego	[6, 7]
ATL	L17F12 (anti-Leu-1)/IgG_{2a}	Leu-1	1	Renal, hepatic (transient)	Transient reduction in circulating cells	Stanford	[8]
CTCL	L17F12/IgG_{2a}	Leu-1	6	Dyspnea, hives, cutaneous pain	Minor remission in 5 out of 7 patients	Stanford	[9, 10]
CTCL	T101/IgG_{2a}	T65	12	Dyspnea, fever (101°–102° F)	Minor remission in 4 patients	NCI	[11]
CTCL	T101/IgG_{2a}	T65	4	Dyspnea, fever	Minor remissions	U. Calif. San Diego	[7]
T-ALL	L17F12/IgG_{2a} 12E7/IgG_1 4H9/IgG_{2a}	Leu-1 T & B cells T cells	8	Sporadic coagulopathy	Transient reduction in circulating cells	Stanford	[12]
cALL	J5/IgG_{2a}	CALLA	4	Fever (101°–102° F)	Transient reduction in circulating cells	Dana-Farber	[13]
AML	PM/81/IgM AML-2-23/ IgG_{2b} PMN 29/IgM PMN 6/IgM	NR^+ NR NR NR	3	Fever, back pain, arthralgia, myalgia	Transient reduction in circulating cells	Dartmouth	[14]
Gastro-intestinal	17-1A/IgG_{2a}	NR	20	Urticaria, bronchospasm, mild hypotension	Limited response	Wistar/ Fox Chase	[15, 16]
Melanoma	9.2.27/IgG_{2a}	250K	20	Fever, serum sickness	None	NCI	[17]
Melanoma	R25/IgG_3	G_{D3}	12	Urticaria, pruritis, fever, wheezing, vomiting	Major tumor regressions in 3 patients	Memomrial Sloan-Kettering	[18]

cALL, common acute lymphoblastic leukemia; ATL, adult T-cell leukemia-lymphoma; CTCL, cutaneous T-cell lymphoma; B-CLL, B-chronic lymphocytic leukemia; AML, acute myelogenous leukemia. NR, not reported.

of monoclonal antibodies, and others have developed hypotension and tachycardia. A limited number of patients have developed transient reduction in their creatinine clearance and elevation of their liver enzymes, thought to be secondary to immune complexes. In conclusion, murine-derived monoclonal antibodies can be safely infused; although side effects can be expected, they are usually mild.

Another attractive therapeutic application of monoclonal antibodies is to "clean up" autologous bone marrow prior to bone marrow transplantation. Patients who are in clinical remission will often have morphologically undetectable tumor cells in their bone marrow which theoretically could be detected and destroyed with specific antibodies and complement (or antibodies conjugated to toxins). Most of the obstacles and toxicities with monoclonal antibody infusion would be eliminated by using this technology. Such an approach has been reported when using the B1 monoclonal antibody to clean up autologous bone marrow from patients with non-Hodgkin lymphoma [19] and a variety of antibodies to clean up bone marrow from patients with acute lymphoblastic leukemia [20, 21]. Early results have demonstrated that bone marrow reconstitution takes place in virtually every patient. Therapy is tolerated quite well, and most of the patients will enter a complete remission. However, for acute lymphoblastic leukemia only one-third of the patients have been maintained for more than 1 year in remission, and this is not different from what is seen in allogeneic bone marrow transplantation. The results for non-Hodgkin lymphoma are more promising, with over 50% of the patients remaining in remission with a median duration of 22 months. Long-term disease-free survival will be necessary before concluding that these therapies have been curative.

Antibodies conjugated to drugs, toxins, and radionuclides can be used for therapy and radioimaging. There is considerable evidence, at least in animal tumor models, suggesting that antibodies covalently linked to certain toxins such as ricin or diphtheria toxin have a greater antitumor effect both in vitro and in vivo than unconjugated free antibodies [22, 23]. A number of centers are currently studying monoclonal antibodies conjugated to radionuclides such as ^{111}In or ^{131}I to determine diagnostic efficacy in man.

C. Interferon

Interferons are a family of proteins produced by cells in response to virus, double-stranded ribonucleic acid, antigens, and mitogens. In addition to antiviral activity, the interferons have profound effects on a number of components of the immune system, including B cells, T cells, natural killer cells, and macrophages, and have antiproliferative activity. With respect to the interferons and cancer therapy, it is still unclear whether the interferons work primarily by their antiproliferative activity or through alterations of immune responses. It is clear, however, from both preclinical and clinical studies that interferons have antitumor activity in a number of tumor systems [29].

The most extensively studied interferons clinically are the natural and recombinant interferon-α preparations (Table 2). Antitumor activity for the alpha interferons has been quite limited in regard to solid tumors. The best results have been achieved in AIDS-related Kaposi's sarcoma, with approximately a 50% response rate [30, 31]. Results for breast cancer have been mixed, with 30%–40% responses reported in some studies and no responses in others [32–34]. Renal cell carcinoma is among the tumors most unresponsive to any known cytotoxic agents, and approximately a 15% partial response rate to interferon-α has been reported [35]. Partial response rates of around 10%–20% have been reported for patients with melanomas, similar to the chemotherapy response rates [36, 37]. Responses for other common solid tumors such as bronchogenic carcinoma and colon cancer have been negative. Preliminary trials with crude interferon-α preparations from Yugoslavia suggested some activity for head and neck cancers; however, these results have not been confirmed outside Yugoslavia.

The most impressive results for interferon-α have been obtained in the hematologic malignancies. Approximately 50% response rates for patients with low-grade

Table 2. Clinical trials with interferon-α[a]

Tumor	Number of evaluable patients	Response rates			Total response %
		CR[a]	PR[a]	MR[a]	
Hematologic malignancies					
Hairy-cell leukemia	121	14[b]	69	35	95
Non-Hodgkin lymphoma (low-grade)	92	9	30	6	42
Non-Hodgkin lymphoma (intermediate- and high-grade)	36	1	4	2	14
Cutaneous T-cell lymphoma	20	2	7	2	45
Chronic lymphocytic leukemia	67	0	12		18
Multiple myeloma	177	3[b]	18		17
Chronic myelogenous leukemia	68	2	46	7	81
Essential thrombocythemia	4	3	0		75
Acute leukemia	62		19[c]		31
Solid Tumors					
Kaposi's sarcoma (AIDs-related)	44	9	12		48
Osteogenic sarcoma	15	0	1		7
Melanoma	167	6	13	2	11
Renal cell	252	6	37	28	17
Breast	187	0	14	10	7
Ovarian	42	5	3		19
Bladder (papillomatosis or superficial)	20	10	8		90
Colorectal	66	0	2		3
Carcinoid	9	0	6		67
Lung, small-cell	10	0	0		0
Lung, non-small-cell	70	0	1		1

[a] Special thanks to Dr. Mark Roth for compiling the data shown in this table. CR, complete response; PR, partial response; MR, minor response. Complete response means absence of hairy cells in the bone marrow (in most studies) and normalization of peripheral blood white cells, platelets, and erythrocytes. Partial response means a normalization of peripheral blood white cells, platelets, and erythrocyte counts, and > 50% reduction in hairy cells in the bone marrow. Minor response generally means improvement in hemoglobin to more than 10 g/dl or improvement in platelets to more than $100 \times 10^9/1$ or improvement in neutrophils to more than $1 \times 10^9/1$.

[b] Complete response and partial response not available from all trials; % total response includes all responses.

[c] Most responses were of short duration.

non-Hodgkin lymphoma and cutaneous T-cell lymphoma have been reported [38–41]. These responses have lasted from 6–10 months, and in many patients, responses have continued for a number of years. Patients with chronic lymphocytic leukemia have been reported to have approximately an 18% response rate, and in our trials at the National Cancer Institute (NCI) we reported only two brief responses among 18 evaluable patients [42].

We and other investigators have reported excellent responses for patients with hairy-cell leukemia treated with recombinant leukocyte A interferon [43–46]. Responses appear to be equivalent for patients who have not had prior splenectomy. Greater than 90% response rates have been widely reported. While complete responses are not common (careful evaluation of the bone marrow usually reveals residual hairy cells), partial responses and even minimum responses usually lead to a dramatic improvement in blood counts. We also reported immunologic improvement, with natural killer cell activity returning in most patients fol-

lowing therapy with interferon, as well as normalization of T-lymphocyte subpopulations.

Chronic myelogenous leukemia also appears to be responsive [47] to interferon-α, with hematologic remission reported in 55 out of 68 patients (81%). These patients have had improved hematologic parameters as well as reduction in size of enlarged spleens and suppression of the Ph^1 chromosome.

These studies have demonstrated that interferon-α has the highest reported response rate for any standard or experimental agent in advanced, previously treated cutaneous T-cell lymphoma patients. They also establish interferon-α as a new non-cross-resistant modality of therapy for low-grade- and possibly intermediate-grade-histology non-Hodgkin lymphoma. Interferon-α may be the most active single agent for hairy-cell leukemia and should be considered first for therapy when splenectomy is no longer effective in controlling the disease. Whether 2′-deoxycoformycin is more effective than interferon-α for hairy-cell leukemia remains to be determined. Phase III trials for previously untreated patients with non-Hodgkin lymphoma, cutaneous T-cell lymphoma, and hairy-cell leukemia, and chronic myelogenous leukemia patients are clear avenues of future investigation.

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