FUTURE ONCOLOGY

TECHNOLOGY, PRODUCTS, MARKETS AND SERVICE OPPORTUNITIES

A NEW MEDICINE PUBLICATION | MARCH 1996 | VOLUME 1, NUMBER 11

STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

NEW TREATMENT APPROACHES FOR HEMATOLOGIC MALIGNANCIES-LEUKEMIA, LYMPHOMA AND MULTIPLE MYELOMA

MEETING COVERAGE

ADVANCES IN BREAST CANCER TREATMENT

A REPORT FROM THE SIXTH INTERNATIONAL CONGRESS ON ANTI-CANCER TREATMENT (ICAT), PARIS, FRANCE, FEBRUARY 6-9, 1996

COPYRIGHT © 1996 NEW MEDICINE, INC. UNAUTHORIZED PHOTOCOPYING, DISTRIBUTION OR ELECTRONIC STORAGE IS PROHIBITED BY LAW.

STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

NEW TREATMENT APPROACHES FOR HEMATOLOGIC MALIGNANCIES-LEUKEMIA, LYMPHOMA AND MULTIPLE MYELOMA

NEW STRATEGIES FOR THE TREATMENT OF HEMATOLOGIC MALIGNANCIES

Approved methodologies and novel approaches in development for treatment of hematologic malignancies involve mostly drug therapy and radiotherapy, but bone marrow ablation, with subsequent rescue using hematopoietic cell transplants, is also proving useful in relapsed disease. Although most hematologic malignancies, with the exception of non Hodgkin's lymphoma (NHL), are relatively rare, they present a potentially large market for drug-based therapies that are used almost invariably as first-line treatment and, also, for maintenance, in relapse and for rescue. A patient with a hematologic malignancy may be under drug treatment until cured or expires, sometimes for as long as three years. In view of the global opportunity for drugs to treat hematologic malignancies (see Exhibit 1), numerous agents are in development (see Exhibit 2). Not included in this discussion are adjunctive therapies and drugs/devices used in *ex vivo* cell processing, bone marrow purging and transplantation of hematopoietic cells.

Leukemia

In spite of several novel drugs having entered the clinic recently, outcomes of leukemia patients are disappointing, remissions are short-lived, and only a relatively small percent of patients survive past five years. However, several new approaches have somewhat improved the short-term outlook for leukemia patients. For instance, manipulations of induction regimens have increased remission rates in acute myelocytic leukemia (AML) and contributed to improved long term survival. One approach that has been used successfully in failed chemotherapy patients, and is now being increasingly used to sustain remissions, is transplantation of bone marrow (BMT) and/or peripheral blood stem cells (PBSCT). Leukemia represents the most common indication for allogeneic BMT (alloBMT), accounting for 74% of all such transplants worldwide, 73.4% in the USA and 75.4% in Europe, in 1993 (see FO, V1 #9, pp 209-215).

Lymphoma/Multiple Myeloma

Chemotherapy, radiation therapy and BMT are standard therapies for lymphoma/multiple myeloma. This group of diseases is second only to leukemias as an indication for BMT (see FO, V1 #10, pp 226-231).

Hodgkin's Disease

The most promising treatment approaches in Hodgkin's disease (HD) involve biologic modalities, such as the use of isotopic immunoglobulins directed against ferritin and monoclonal antibodies (MAbs) targeting interleukin-2 (IL-2), which is expressed on HD cells. In five consecutive clinical studies, 134 patients with recurrent HD were treated by radioimmunotherapy (RIT) at M. D. Anderson Cancer Center (Houston, TX), using IV antiferritin labeled with iodine-131 (^{131}I) or indium-111 (^{111}In) for diagnostic purposes, and yttrium-90 (^{90}Y) for therapeutic purposes. Overall response rate among patients with recurrent, end-stage HD, treated with ^{90}Y-labeled antiferritin, was 60%, with 50% being complete responses (CRs). Patients achieving CR survived significantly longer than partial responders (2 years versus 1 year). Results with ^{90}Y-labeled antiferritin were significantly better than those with ^{131}I-labeled antiferritin. RIT, a low-toxicity, low-cost, outpatient procedure for recurrent HD, elicits a high response rate in patients with unfavorable prognosis (Vriesendorp HM, etal, Cancer Research, 1995 Dec 1, 55(23 Suppl):5888s-5892s).

Non Hodgkin's Lymphoma

Biologic therapies also represent promising treatment approaches for NHL, particularly low-grade lymphoma, because the indolent nature of the disease selects for patients who are relatively healthy and have a sufficiently long life expectancy to allow time to respond to the agent being tested. Numerous agents are in phase III trials for this indication, most prominent among them various MAb-based therapeutics.

Multiple Myeloma

New treatment approaches for multiple myeloma are based on new insights into the disease. A hallmark of the various phases of multiple myeloma is a dysregulated cytokine network. For instance, IL-6, a hematopoietic cytokine, was shown to promote growth of myeloma cells, and serum IL-6 levels have been shown to correlate with prognosis. One treatment approach, therefore, involves neutralizing IL-6 *in vivo*, using anti-IL-6 MAbs. However, none of the patients treated with this method achieved remission or improved outcome as judged by standard clinical criteria (Bataille R, etal, Blood, 1995 Jul 15, 86(2):685-91). Another interleukin implicated in multiple myeloma is IL-1β. Aberrant expression of IL-1β which is a known osteoclast activating factor, can alter expression of IL-6. IL-1β also regulates expression of adhesion molecules that may enable malignant cells to home to the bone marrow (Lacy, MQ, etal, Blood, Vol 86, No 10, Supplement to Nov 15, 1995, Abs. 215). In contrast, interferon-γ (IFN-γ) was shown to be an inhibitor, of *in vitro,* proliferation of an IL-6-dependent myeloma cell line. This antiproliferative effect appears to be caused mainly by inhibition of IL-6 (Palumbo A, etal, Leukemia and Lymphoma, 1995 Jul, 18(3-4):215-9).

Mechanisms associated with osteolytic bone destruction, one of the hallmarks of multiple myeloma, are poorly understood. Investigators at VA Medical Center and the

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

University of Texas (San Antonio, TX) cloned a novel osteoclast stimulatory factor (OSF) expressed by bone marrow cells. This clone was shown to be a novel gene by sequence analysis with no homology to any known cytokine (Alsina M, etal, Blood, Vol 86, No 10, Supplement to Nov 15, 1995, Abs. 213).

EXTENSIONS AND REFORMULATIONS OF EXISTING DRUGS

Conventional chemotherapy usually results in high initial response but many patients with hematologic malignancies invariably relapse within a short period of time. Relapsed disease is almost uniformly fatal. Numerous drug combinations are being clinically evaluated in relapsed hematologic malignancies, with varying success but, to date, none has affected a cure. Interestingly, because of the dearth of new agents, developers are resurrecting older drugs that may be reformulated or administered under alternative regimens to improve effectiveness and/or mitigate toxicities. Reformulations of existing drugs employing various drug delivery technologies, also represent creative solutions breathing new life into drugs of limited use because of poor pharmacokinetics, difficult administration requirements, and serious toxicities. For instance, using a proprietary liposome encapsulation technology, Sequus Pharmaceuticals (Menlo Park, CA) has developed and is evaluating new versions of such often used anticancer drugs as doxorubicin (Doxil; approved in the USA for the treatment of Kaposi's sarcoma in November 1995), vincristine and cisplatin.

Ilex Oncology (San Antonio, TX), a private company, is developing two drugs for the treatment of hematologic malignancies. In March 1996, Ilex initiated a phase I clinical trial with aminopterin (AMT) in children with acute lymphocytic leukemia (ALL) who are unresponsive to the standard chemotherapy drug, methotrexate (MTX). Ilex purified and reformulated AMT, one of the first chemotherapy drugs to be used in childhood ALL, that was subsequently abandoned as newer, less toxic drugs became available. Ilex believes that better manufacturing methods should improve the clinical profile of AMT. Another drug, mitoguazone (MGBG), a polyamine biosynthesis inhibitor, discarded in the 1960s because it caused severe mucositis and other toxicities, was resurrected in the late 1970s. Using a weekly administartion schedule, the drug was effective and well tolerated in clinical trials in refractory HD and NHL. MGBG is nonmyelosuppressive, crosses the blood brain barrier and appears to work better in malnourished patients, such as those with AIDS-related lymphoma, probably because of polyamine depletion associated with inanition. Currently, MGBG is in a phase III pivotal multicenter clinical trial for the treatment of refractory/relapsed AIDS-related lymphoma. The drug has been licensed to Sanofi Winthrop worldwide, in exchange for project funding, milestone payments and royalties.

BIOLOGIC THERAPIES

Monoclonal Antibodies/ Immunoconjugates/Immunotoxins

MAb-based treatment approaches are making a strong comeback after years of disappointing results. Used alone or in combination with radioisotopes, immunotoxins or drugs, better engineered MAbs are proving clinically useful in the treatment of various hematologic malignancies. Actually, MAb-based agents are the only biologic therapies in phase III trials for hematologic malignancies. However, in most cases MAbs serve as drug delivery vehicles, targeting cell killing agents to tumor cells and not as therapeutics in their own right. Also, with several of the radioimmunoconjugates, hematopoietic cell transplants are required to rescue patients administered high doses of the radioimmunoconjugate that is necessary to elicit a response.

A promising approach using unconjugated MAbs as therapeutic agents is an anti-CD20 MAb, which depletes malignant and mature normal B cells, in development by IDEC Pharmaceuticals. A notable failure among unconjugated MAbs is that of Campath-1H, which was in phase II clinical trials in NHL, sponsored by Glaxo Wellcome.

Celltech (Slough, Berkshire) is developing, jointly with American Home Products (Lederle), CDP-771, a recombinant humanized MAb linked to calichaemicin that binds to CD33, the specific antigen present on myeloid progenitor cells. The agent was in phase I/II clinical trials in the treatment of AML as of mid-summer 1995.

Coulter (Miami, FL) is clinically evaluating ^{131}I-B1 (anti-CD20) MAb therapy with autologous stem cell transplantation rescue for relapsed B cell lymphomas. In a 25-patient phase II clinical trial of relapsed B-cell lymphoma, 18 of the 21 treated patients achieved objective responses, including 16 CRs. One patient died of progressive lymphoma and one died of sepsis. Analysis of phase I and II trials reveal a progression-free survival of 62% and an overall survival of 93% with a median follow-up of 2 years. This therapy produces CRs of long duration in most patients with relapsed B-cell lymphomas when given at maximally tolerated doses, followed by autologous stem cell rescue (Press OW, etal, Lancet, 1995 Aug 5, 346(8971):336-40).

IDEC Pharmaceuticals (San Diego, CA) is focusing on the development of MAb-based approaches to treat cancer and immune-mediated disorders. Its lead product is IDEC-C2B8, currently in phase III trials as an adjunct for the treatment of B cell NHL. IDEC-C2B8, an anti-CD20 chimeric MAb (pan-B), targets CD20 antigen present on mature B cells and B cell tumors but not on B cell precursors or on plasma cells. IDEC-C2B8 was shown to deplete mature normal and malignant B cells by:

- binding to the CD20 receptor and inhibiting B cell growth

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

- activating the complement system, resulting in cell lysis via complement-dependent cytotoxicity (CDC)
- activating macrophages
- recruiting killer cells via antibody-dependent cellular cytotoxicity (ADCC)

IDEC-C2B8 was also shown to induce apoptosis and sensitize drug-resistant tumors to the effects of platinum-based agents, etoposide and ricin. IDEC-C2B8 causes rapid B cell depletion within 24 to 72 hours after infusion, that persists with recovery in 5 to 7 months. It is currently evaluated as second line therapy and in combination with other agents. In March 1996, IDEC announced that it had completed patient accrual for a phase III multicenter (30 institutions) open label, single arm trial of IDEC-C2B8 as monotherapy for the treatment of relapsed low-grade or follicular NHL. IDEC-C2B8 is administered by IV infusion on an outpatient basis over 22 days.

In a phase I/II clinical trial of 47 pretreated patients with relapsed NHL, 37 patients were treated with IV infusion of 375 mg/m^2 (weekly x 4). In 34 evaluable patients with low grade or follicular NHL, use of this regimen resulted in a CR rate of 9%, a PR rate of 41% and an overall response of 50%. The median time to progression was 10 months, with the longest response over 20 months. Therapy was well tolerated (Maloney DG, etal, Proc of ASH 1995, Abs. 205). Interesting results were also reported when this antibody was given in conjunction with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy to patients with low-grade NHL. The overall response rate was 100% (11 CR and 3 PR), with a complete response rate of 79%. Also, four patients known to be positive for bcl-2 prior to therapy were bcl-2 negative after completing the regimen (Czuczman MS, etal, Proc of ASH 1995, Abs. 206). However, these results must be interpreted with caution, because they involved only 14 patients, 75% of whom had not received prior therapy. This high response rate may be due to CHOP therapy alone. However, it is an interesting approach because the two therapies do not have overlapping toxicity, they act by different mechanisms and may have a synergistic effect.

IDEC is also clinically evaluating IDEC-Y2B8, anti-CD20 murine MAb conjugated to ^{90}Y, for the treatment of relapsed NHL and to ^{111}In (IDEC-In2B8), for imaging. In a phase I trial using single doses of IDEC-Y2B8, among 17 pretreated patients, there were 4 CRs (28%), 5 PRs (36%), and disease stabilized in 5 patients. Time to progression for the nine responders ranged from 5.9 to 13.4 months. Recommended dose for phase II studies is ≤40 mCi. Use of ^{90}Y is deemed superior to ^{131}I because of its higher energy, pure β emissions, longer β path length and shorter half-time (64 hours). Also, ^{90}Y immunoconjugates may be delivered in the outpatient setting (Grillo-Lopez AJ, etal, Proc of ASH 1995, Abs. 207).

IDEC is developing anti-CD20 MAb therapies in collaboration with Genentech (South San Francisco, CA). In March 1995, IDEC entered into a collaborative agreement with Genentech worth approximately $57 million in cash and equity, if all milestones are reached as specified. Genentech made payments of $11.5 million to date. Under terms of the agreement, IDEC and Genentech are to co-promote IDEC-C2B8 in the USA and Canada. Genentech has obtained exclusive rights elsewhere in the world, and will pay royalties to IDEC, estimated at 12% on sales. In December 1995, Genentech granted exclusive rights to Zenyaku Kogyo (Tokyo, Japan) to develop and distribute IDEC-C2B8 in Japan. In February 1996, Genentech exercised its option which it had secured in the March 1995 agreement, to expand its collaboration with IDEC to include clinical development and commercialization of IDEC-Y2B8. In addition, Genentech will pay IDEC $1.5 million as an option fee and reimburse costs of phase II trials of up to $1.5 million. Other terms of this agreement are under negotiation.

ImmunoGen (Cambridge, MA) is developing immunoconjugates (immunotoxins), composed of antibodies targeting various antigens on tumor cells. The company's lead product is Oncolysin B consisting of anti-B4 MAb which targets CD19-positive cells, linked to blocked ricin (a ricin molecule chemically modified so that the lectin binding sites of the B-chain have been blocked by covalent attachment of affinity ligands). Oncolysin B entered phase III clinical trials in July 1993 in relapsed lymphoma following autologous bone marrow transplantation (autoBMT) to eradicate minimal disease. This indication was selected because it was found that patients most likely to benefit from treatment with this agent were those without bulky disease. Trial endpoints include time to relapse of patients in CR treated by Oncolysin B compared to controls. Results are not expected until 1998, at the earliest. Oncolysin B was also evaluated in phase II trials in patients with B cell malignancies in remission after treatment with conventional chemotherapy. A phase I/II clinical trial of Oncolysin B in combination with conventional chemotherapy in AIDS-related lymphoma was completed in September 1995. Immunogen intends to seek approval for Oncolysin B for all patients with B cell malignancies who achieve remission. A phase II trial is currently underway using this drug with EPOCH (four drugs in CHOP, plus etoposide) chemotherapy. To date there has been an approximate 33% response rate (personal communication, 1996). In preclinical *in vitro* and *in vivo* studies, combinations of anti-B4-bR with such conventional chemotherapeutics as doxorubicin or etoposide increased tumor cell killing and increased the life span of the mice by 129% and 115%, respectively. B4-bR may also play a role in treatment of cancer at the minimal residual disease stage, when cells become resistant to chemotherapy (O'Connor R, Blood, 1995 Dec 1, 86(11):4286-94).

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

ImmunoGen was granted an exclusive worldwide license from Dana-Farber Cancer Institute (Boston, MA) in May 1981, covering the development of MAb, toxin, and drug immunoconjugates. ImmunoGen has developed several other immunotoxins for hematologic and other malignancies but the company was forced to scale down its activities to focus on Oncolysin B and to conserve cash. Further development of these products will be undertaken only if the company secures third-party support. Products whose development is on hold include:

- Oncolysin M, an anti-My9 MAb conjugated to blocked ricin, for *ex vivo* bone marrow purging
- Oncolysin CD6, a high affinity anti-CD6 antibody conjugated to blocked ricin, that is a potent anti-pan T cell immunotoxin capable of killing cells in an antigen dependent manner; was in phase I clinical trials for relapsed T cell malignancies
- Anti-B4-DC1, a small drug immunoconjugate consisting of anti-B-4 MAb linked to a potent synthetic small drug effector molecule, DC1; an IND was granted to begin clinical trials; a patent covering therapeutic use of analogs and derivatives of DC1, was awarded in December 1995; in preclinical studies, median increase in survival of animals treated with anti-B4-DC1 was 170% compared to untreated controls, representing six logs of cell kill, compared to 1-3.4 logs of cell kill for conventional chemotherapeutics (Chari RV, etal, Cancer Research, 1995 Sep 15, 55(18):4079-4084)

Immunomedics (Morris Plains, NJ) is clinically evaluating a MAb radioconjugate consisting of MAb LL2 linked to either ^{131}I or ^{90}Y. Various forms of the antibody, murine, humanized or F(ab')2 fragment, have been evaluated in phase I clinical trials. This MAb immunoconjugate is intended for the treatment of NHL. In two clinical trials, 25 patients were treated using different doses of various forms of Immunomedics' LL2 immunoconjugate against NHL. In one of the trials involving low radiation doses, 6 of 17 patients with advanced disease showed a tumor response. A clinical trial using higher doses is in progress.

Medarex (Annandale, NJ) is developing "bispecific antibodies" (Bispecifics) constructed by fusing two antibody fragments, each of which is specific for a different site. The "trigger" fragment, which is a humanized antibody fragment proprietary to Medarex, is specific for the Fc receptor and binds to, and triggers, a macrophage. The "target" fragment, which is licensed to Medarex by Dartmouth University (Dartmouth, NH), is specific for a particular antigen on a tumor cell or a pathogen. Bispecifics are designed to bind to a specific type of tumor cell or pathogen and to a killer cell, triggering the destruction of the target by the killer cell. Medarex is currently developing two therapeutic products, MDX-11, and MDX-22, both designated orphan drugs, for the treatment of AML. MDX-11 specifically binds to leukemia cells and is designed to cause their destruction by triggering the body's natural complement system. In a multicenter phase I/II trial of 16 patients with advanced or secondary AML, MDX-11 was generally well tolerated. Treatment with MDX-11 alone caused the destruction of an average of 90% of circulating leukemia cells in 50% of treated cases. Phase II clinical trials of MDX-11 commenced during 1994. MDX-22 has been under evaluation since 1983, as an *ex vivo* bone marrow purging approach in BMT.

Protein Design Labs (PDL; Mountain View, CA), founded in 1986, is developing human and computer-designed SMART (humanized) MAbs that have a longer half-life and are less immunogenic than traditional murine MAbs. SMART HuM195, a humanized IgG_1 version of murine MAb 195 reactive with the early myeloid surface antigen CD33, is in multicenter phase II/III USA trial, in the treatment of AML, which began in June 1994. Both conjugated and unconjugated versions of M195 have been evaluated. In a clinical study of unconjugated HuM195 in acute promyelocytic leukemia (APL) patients in remission (6 in first and 2 in second remission) post retinoid therapy, all patients experienced CR lasting from 3+ to 14+ months. Patients received six doses of the drug (3 mg/m^2 per dose) twice weekly for three weeks. Following this, only patients in first remission were treated with idarubicin and cytarabine. All patients then received monthly maintenance with two doses of HuM195 3 to 4 days apart. Side effects were manageable; no hematologic toxicity was observed and human anti-mouse antibody (HAMA) response was not a problem. Using reverse transcription-PCR (RT-PCR), it was shown that five of eight patients with RT-PCR-detectable disease before treatment converted to negative after HuM195 therapy (Jurcic JG, etal, ASH95, Abs. 2057).

In September 1995, PDL initiated a phase I clinical trial of SMART M195 in Japan in 16 patients with AML. According to the study's protocol, groups of four patients are administered one of four dose levels for a total of 7 doses over a period of four weeks. The Japanese clinical trial is being sponsored by Kanebo (Osaka, Japan) which licensed Asian marketing rights to SMART M195. The antibody drug material being used in the study is manufactured at PDL's Plymouth, MN, facility.

Seragen (Hopkinton, MA), using recombinant DNA techniques, has constructed various tumor-selective fusion toxins by replacing the native diptheria toxin receptor-binding domain with one of a variety of cytokines. The IL-2 receptor-targeted fusion toxin, DAB_{389}IL-2, is in a 22-center phase III clinical trial in cutaneous T cell lymphoma (CTCL) and in phase II trials in NHL. In a phase II multicenter dose-escalation trial, the drug was associated with a 50-100% reduction in tumor burden in 12 of 32 CTCL patients. Seven of 10 CTCL patients, the majority with stage I or II disease, treated at the University of Alabama (Birmingham, AL)

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

Exhibit I
Patients with Hematologic Malignancies Treated Annually by Chemotherapy in the USA and Worldwide

	USA								
	Induction Therapy (#)	Total (%)	Relapsed Patients (#)	Terminal/ Rescue (#)	Mortality (#)	5-year Survivors (#)	Rate (%)	BMT/ Other (#)	Total Chemo Candidates (#)
LEUKEMIA									
Lymphocytic	11,000	42.8	17,198	5,591	6,400	6,955	63.2	733	34,522
ALL	3,933	35.8	5,882		2,105	2,057	52.3	733	
B-ALL	3,343	85.0							
T-ALL	590	15.0							
CLL	6,403	58.2	10,454		3,842	4,399	68.7		
B-CLL	6,083	95.0							
T-CLL	320	5.0							
Other	664	6.0	921		342	207	31.2		
Myelocytic	11,100	43.2	16,279	6,524	8,400	1,721	15.5	2,416	36,319
AML	6,029	54.3	8,496		5,500	327	10.4	1,411	
CML	3,272	29.5	5,244		2,579	775	23.7	1,005	
Other	1,799	16.2	2,597		324	327	18.2		
Other/ unspecified	3,600	14.0	5,302	5,086	5,600	1,030	28.6	325	14,313
TOTAL	25,700	100.0	38,779	17,201	20,400	9,843	38.3	3,474	85,154
LYMPHOMA									
HD	7,800	11.0	9,222	808	1,510	6,150	78.8	682	18,512
NHL	50,900	71.5	74,573	8,030	23,300	26,468	52.0	1,824	135,327
by cell type									
B Cell	38,175	75.0							
T Cell	1,527	3.0							
null-cell	11,198	22.0							
by grade									
low-grade	11,311	22.2							
intermediate-grade	21,624	42.5							
high-grade	6,321	12.4							
unclassified	11,644	22.9							
MULTIPLE MYELOMA	12,500	17.5	23,682	6,600	10,400	3,463	27.7	353	43,135
TOTAL	71,200	100.0	107,477	15,438	35,210	36,081	50.7	2,859	196,974

— continued on next page

experienced CR. DAB_{389}IL-2 is administered intravenously as a daily 15-minute infusion for five days every three weeks, repeated for up to six courses. Under the terms of an agreement entered in 1994, Eli Lilly has exclusive rights, except in certain Asian countries, to IL-2 fusion toxin for the treatment of cancer. Other fusion toxins with potential cancer applications, in preclinical development include IL-6 fusion toxin for multiple myeloma and IL-4 fusion toxin for hematologic malignancies expressing the IL-4 receptor.

Techniclone International (Tustin, CA) has also developed and is clinically evaluating a radioimmunoconjugate, Oncolym, against B cell NHL. Oncolym consists of Lym-1 MAb conjugated to ^{131}I (^{131}I-Lym-1). A multicenter phase III trial of Oncolym which began in

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

Exhibit 1 (continues)

WW (NORTH AMERICA, EUROPE* AND JAPAN)									
	Induction Therapy (#)	Total (%)	Relapsed Patients (#)	Terminal/ Rescue (#)	Mortality (#)	5-year Survivors (#)	Rate (%)	BMT/ Other (#)	Total Chemo Candidates (#)
LEUKEMIA									
Lymphocytic	37,386	48.6	58,625	16,410	25,000	23,628	63.2	2,365	114,786
ALL	13,477	36.1	20,154			7,048	52.3	2,365	
B-ALL	11,455	85.0							
T-ALL	2,022	15.0							
CLL	21,612	57.8	35,284			14,847	68.7		
B-CLL	20,531	95.0							
T-CLL	1,081	5.0							
Other	2,297	6.1	3,187			717	31.2		
Myelocytic	39,533	51.4	57,711	22,505	36,813	6,128	15.5	7,735	127,484
AML	20,709	52.4	28,976			2,154	10.4	3,792	
CML	9,818	24.8	15,734			2,327	23.7	3,024	
Other	9,006	22.8	13,001			1,639	18.2	919	
TOTAL	76,919	100.0	116,336	38,915	61,813	29,460	38.3	10,100	242,270
LYMPHOMA									
HD	28,062	16.2	33,181	2,890	3,321	22,113	78.8	1,567	65,700
NHL	113,177	65.4	164,899	20,849	54,802	58,852	52.0	3,935	302,860
by cell type									
B Cell	84,883	75.0							
T Cell	3,395	3.0							
null-cell	24,899	22.0							
by grade									
low-grade	25,150	22.2							
intermediate-grade	48,080	42.5							
high-grade	14,055	12.4							
unclassified	25,981	22.9							
MULTIPLE MYELOMA	31,849	18.4	60,341	15,228	24,910	8,822	27.7	1,538	108,956
TOTAL	173,088	100.0	258,421	38,967	83,033	89,697	51.9	7,040	477,516

** Excludes the former USSR*

January 1996, will enroll up to 130 patients with refractory NHL. In a phase II clinical trial of 50 relapsed patients with high-grade NHL, Oncolym treatment resulted in an overall response of 56%. The product is manufactured by Mills Biopharmaceuticals (Oklahoma City, OK). Under an agreement entered in October 1992, Alpha Therapeutic (Los Angeles, CA), a wholly-owned subsidiary of Green Cross (Osaka, Japan), is financing phase III trials and has marketing rights in USA, Asia and certain European countries. In March 1996, Techniclone entered into an exclusive distribution agreement with Biotechnology Development (Miami, FL) in geographic areas not covered by Alpha Therapeutic. Under the agreement Techniclone received a cash payment of $3 million and retains the worldwide manufacturing rights.

University of Minnesota (Minneapolis, MN) investigators, led by Dr. Fatih Uckun, in collaboration with Bristol-Myers Squibb Pharmaceutical Research Institute (Princeton, NJ) researchers, developed a conjugate consisting of the enzyme inhibitor genistein and MAb B43, which targets the CD19 molecule expressed on B cell precursor (BCP) leukemia cells. BCP leukemia is the most

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

common type of childhood cancer and the second most common form of adult acute leukemia. In preclinical studies this agent bound with high affinity to BCP leukemia cells, selectively inhibited CD19-associated tyrosine kinases and induced rapid apoptosis. At dose levels less than one tenth of the maximum tolerated dose (MTD), 100% long-term event-free survival was achieved in the treated animals, compared with zero survival in controls. Treatment was well tolerated with no instances of systemic toxicities (Uckun FM, etal, Science, 10 Feb 1995, 267:886-891). BMS is not developing this agent. Genistein is a naturally occurring protein tyrosine kinase inhibitor that specifically inhibits several receptor and cytoplasmic tyrosine kinases, including p210bcr-abl.

Immunization/Vaccines/Gene Transfer

Another biologic therapy approach, currently being pursued by many developers for most malignancies is immunization. Numerous cancer vaccines are in development based on various immunization approaches including nonspecific immunotherapy (activation of macrophages, natural killer (NK) cells and other nonspecific effectors using microbial or chemical immunomodulators or T cells activated secondarily through macrophages) and specific immunotherapy (activation of specific effector cells and "armed" macrophages using antigenic tumor cells, cell lysates, or extracted tumor antigens); adoptive immunotherapy, involving transfer of immunological cells or informational molecules; and passive immunotherapy, involving transfer of antibodies or antisera, providing exogenous immunity.

Among specific immunotherapy approaches, genetic modification of tumor cells is being used to produce cancer vaccines with more defined biological effects. The two technical approaches to genetically modified human cancer vaccines include *ex vivo* gene transfer of cytokine and other genes into tumor cells followed by reimplantation, and *in vivo* gene transfer of major histocompatibility complex (MHC) class I molecules by direct physical application or injection of the gene to transfect the tumor cells and/or the surrounding normal tissues.

Direct injection of "naked" plasmid DNA into muscle and tumor is relatively inefficient, with a low frequency of integration into host chromosomes. To improve gene transfer efficiencies, a number of molecular conjugates containing DNA and other molecules, such as proteins, antibodies and/or viral or bacterial vectors, have been used. Thus far, however, most clinical protocols have used viral vectors for cellular gene transfer. Yet, use of viral vectors poses several challenges in terms of operation efficiency, versatility, and cost effectiveness. In addition, safety issues related to the use of viral vectors are not completely resolved, and may pose health hazards to cancer patients with depressed immunity.

An alternative to these approaches involves particle mediated gene transfer, a method which has been successfully applied to transfect a wide range of cells both *in vitro* and *in vivo*. Transfection with this approach can be expected to be mostly transient, but integration is possible. The recent refinement of this technology into small, portable "gene gun" devices to shoot particles into tumors should help accelerate the application of this approach in clinical trials (Yang NS and Sun WH, Nature Med, [1995] 1:481). One such gene gun, Accell, being developed by Agracetus (Middleton, WI) uses pulses of compressed helium to project microscopic gold projectiles coated with DNA through the skin into tumor cells at almost supersonic speed in a matter of seconds. In June 1995, the Recombinant Advisory Committee (RAC) of the FDA approved initiation of phase I clinical trials with Accell in metastatic colorectal cancer. Other indications include malignant melanoma, T cell lymphoma, and metastatic breast cancer.

Apollon (Malvern, PA), a privately-owned company was founded in 1992, with an initial 33% stake taken by Centocor (Malvern, PA). Apollon is developing vaccines and other products based on its facilitated DNA injection/delivery technology, which involves the intramuscular injection of a bacterial plasmid containing genes encoding pathogenic antigens combined with a facilitator, bupivacaine. Apollon is evaluating Genevax, a naked DNA vaccine that mimics a live attenuated virus. Genevax incorporates specific sequences of DNA to elicit responses from the immune system. The MHC-l directed peptide, coded for by the DNA vaccine, is then synthesized and processed intracellularly, as though it originated from a tumor cell. The firm filed INDs in late 1994 for intramuscular administration of Genevax for HIV infection and T cell lymphoma. Clinical trials for these two indications, began in mid-1995 in the USA.

Cytel (San Diego, CA), in collaboration with researchers at Memorial Sloan-Kettering Cancer Center (NY, NY), reported evidence of a human immune response elicited by peptides (fusion proteins) expressed by the bcr-abl oncogene in CML. Such peptides may be used as antigens in vaccines for CML. The t(9;22) translocation encountered in CML cells, encodes one of two chimeric P210bcr-abl fusion proteins, comprising products of either the b2a2 or the b3a2 exon junction. These junctional sequences are true tumor specific antigens and may be immunogenic. Although these fusion proteins are located intracellularly, they may be recognized immunologically by T lymphocytes via presentation by MHC molecules. Several peptides were identified that were able to bind with high or intermediate affinity to purified HLA class I molecules. Researchers are now test-ing the ability of these peptides to elicit, *in vitro*, specific, class I restricted, cytotoxic T lymphocytes (CTLs) in HLA matched healthy donors. One such CML breakpoint-derived peptide induced specific CTLs (Bocchia M, etal, ASH95, Abs. 2394).

Stanford University (Palo Alto, CA) researchers recently reported on the use of a tumor specific idiotype

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

vaccine for the treatment of B cell lymphoma (Hsu FJ, etal, Proc of ASH 1995, Abs. 1079). This vaccine is composed of tumor idiospecific protein conjugated to a carrier and mixed with an immunologic adjuvant. Nearly 50% of patients treated with this construct mounted an idiotype-specific immune response. Freedom from progression of disease was prolonged in this group by a median of 4.7 years versus 0.7 years for patients who did not have an immune response.

Vical (San Diego, CA) is developing proprietary technology for the effective administration of polynucleotide and gene-based drug products to deliver therapeutic proteins. In September 1995, Vical announced that it started a phase II clinical trial on Allovectin-7, a gene-based product intended for direct injection into tumor lesions, for treatment of melanoma, lymphoma and kidney, colorectal, and breast cancers. Allovectin-7 contains a gene that encodes a mismatched transplantation antigen (HLA-B7) which, when injected into tumors, causes malignant cells to bear the foreign antigen on their surface. The patient's immune system is then expected to attack and destroy tumor cells expressing the antigen. Allovectin-7 is currently in phase II clinical trial, which commenced in September 1995. The company's other gene-based product for direct injection into tumor lesions, Leuvectin, contains a gene that encodes IL-2. Vical initiated a phase I/II trial at the Arizona Cancer Center (Tuscon, AZ) and at the Scott and White Memorial Hospital (Temple, TX) in April 1995 to evaluate the safety and biological activity of Leuvectin in lymphoma patients (also see FO, V1 #2/3, p 54).

Growth factors/Cytokines

Cytokines function as pleiotropic systemic hormones with overlapping actions on many cell types, acting both as agonists and antagonists. Although they are a vital part of the immune response system, they may also be potentially harmful mediators of inflammation and, possibly, tumorigenesis. Therefore, treatments targeting cytokines that are relatively straightforward to design for *in vitro* tests, are difficult to conceptualize in the systemic milieu.

Cytokines have found many applications in the treatment of hematologic malignancies (see FO, V1 # 9 and 10). Growth factors have been used in several cooperative group studies to improve recovery from chemotherapy and increase dose intensity in AML patients. However, a study of granulocyte-macrophage colony-stimulating factor [GM-CSF; molgramostim; Schering-Plough/Novartis (fomerly Sandoz)] in elderly patients with AML failed to show improved outcome (Stone R, etal, NEJM, 1995, 332:1671-7). A study of granulocyte colony-stimulating factor (G-CSF) in ALL suggested some benefit in older patients, but did not reach statistical significance (CALGB 9111). A study of 76 AML patients randomized to G-CSF (lenograstim; Chugai/ Rhône-Poulenc Rorer) or placebo during induction therapy showed a significant decrease in the time to completion of chemotherapy (39 verses 44 days, p=0.008), but did not show any survival advantage at 20 months (Ottmann OG, etal, Blood, July 15, 1995, 86:444-50).

Immunex (Seattle, WA), however, believes that its recombinant GM-CSF (sargramostim, Leukine) may improve survival in elderly AML patients who experience longer lasting and less tolerated neutropenia after chemotherapy, resulting in higher mortality. Leukine was recommended for approval in April 1995 by FDA's Biological Response Modifiers Committee to stimulate white blood cell production and accelerate white blood cell recovery after induction chemotherapy in AML patients over 55 years-of-age. If approved, Leukine will be the first growth factor commercialized for this indication. Leukine was also approved (in 1991) to accelerate myeloid recovery in autoBMT in hematologic malignancies and, subsequently, to improve survival in BMT failures, and was recommended for approval (in April 1995) in alloBMT. However, the drug failed to gain approval as prophylaxis for neutropenia so that it can compete head on with Amgen's (Thousand Oaks, CA) Neupogen.

Glaxo Wellcome's Wellferon (interferon-α n1, IFN-α n1), prolonged survival of chronic myelocytic leukemia (CML) patients by almost two years compared to standard maintenance therapy. In a multicenter trial, 587 patients with CML in chronic phase were randomized to receive Wellferon or chemotherapy with busulphan or hydroxyurea as maintenance, after initial induction treatment with cytotoxic drugs. The median survival of IFN-α-treated patients was 61 months, compared with 41 months for controls, and 5-year survival was 52% for those on Wellferon, compared to 34% for controls. Although patients positive for the Philadelphia chromosome (Ph^1+) with cytogenetic responses survived longer, all patients on Wellferon survived longer than controls (Allan NC, etal, Lancet, 1995 June 3, 345(8962):1392-7). Wellferon is marketed in the UK for hairy-cell leukemia (HCL).

NOVEL CHEMOTHERAPEUTICS

Retinoids

Retinoids, derivatives of vitamin A, are natural signals that modulate growth and differentiation of normal and tumor cells and induce apoptosis. For instance, it has been shown that drugs which stimulate certain intracellular receptors (IRs) for retinoids induce apoptosis in susceptible tumor cells. Retinoids also induce tumor cells to differentiate into mature cells which do not proliferate abnormally. The degree of differentiation and apoptosis induced by retinoids depends on cell type and differs among retinoid agents. To date, signal transduction pathways involved in retinoid-induced differentiation have not been categorically described. For instance, differentiation of HL-60 cells by all-trans-retinoic acid (ATRA) was shown to be directly mediated by down-regulation of the serine protease myeloblastin (mbn). A 28-kDa heat

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

shock protein (hsp28), previously linked to differentiation of normal and neoplastic cells including HL-60, may be targeted by mbn. Identifying hsp28 as a substrate of mbn strongly suggests that hsp28 may be a key component of the ATRA signaling pathway involved in regulating cell differentiation (Spector NL, etal, Journal of Biological Chemistry, 1995 Jan 20, 270(3):1003-6).

Several retinoids are being developed both for cancer treatment and prevention. Two naturally-occurring endogenous, biologically active retinoids are ATRA and 9-*cis*-retinoic acid. Biologically active chemical analogs of retinoids with activity in leukemia, have also been synthesized. One such analog, 13-*cis*-retinoic acid (isotretinoin) supplied by Roche Laboratories (Nutley, NJ) as Accutane for the treatment of severe acne, induced durable responses in juvenile CML. In a pilot study, among ten children with CML treated by orally-administered isotretinoin (100 mg/m^2 as a single daily dose), two experienced CRs, three PRs, one minimal response and disease progressed in four. Median response duration was 37 months (range 6-83 months) (Castleberry RP, etal, NEJM, Dec 22, 1994, 331(25): 1680-1684).

In November 1995, the FDA approved Roche's Vesanoid, a version of ATRA (tretinoin) for induction therapy of APL (see FO, V1 #9, p 211). ATRA induces granulocyte differentiation in leukemia cells resulting in CR in up to 90% of APL patients with rapid amelioration of the bleeding syndrome. However, orally-delivered ATRA does not maintain adequate plasma and intracellular levels over an extended period of time, in spite of standard dose delivery and even if the dose is increased. ATRA induces its own catabolism *in vivo* by causing an increase in cellular proteins that sequester the compound in the cytoplasm. Low plasma ATRA levels correlate with poor response. Therefore, ATRA can achieve a high remission rate in patients with APL but not a cure, requiring combination with chemotherapy. Also, ATRA is associated with respiratory syndrome, a serious side effect occurring in about 25% of patients.

One of the mechanisms by which retinoids appear to regulate cellular differentiation and proliferation is activation of the retinoic acid receptor (RAR) and the retinoid X receptor (RXR) in the nucleus of cells. Various retinoids are in development based on the premise that their clinical attributes are determined by their receptor binding activity. ATRA binds only to RAR. Retinoids with a different receptor-binding profile and various formulations of ATRA that may be superior to oral ATRA in the treatment of APL and other hematologic malignancies, are in development.

Allergan Ligand Retinoid Therapeutics (ALRT; San Diego, CA), was formed by Ligand Pharmaceuticals and Allergan (Irvine, CA), via issue of 3,250,000 shares of common stock plus warrants at $10 per share in June 1995. ALRT is capitalized at $100 million, with Allergan adding $50 million and Ligand $17.5 million to the proceeds from the offering. ALRT succeeds a joint venture between the two companies set up to develop retinoid compounds for the treatment of cancer and skin and eye diseases.

ALRT's lead compound, LGD-1057 (a chemically synthesized version of 9-*cis* retinoic acid), now referred to as ALRT-1057, is a high-affinity ligand for both RARs and RXRs. In a phase I trial in relapsed patients with APL who were previously treated with ATRA, seven patients were treated with ALRT-1057 at daily oral doses ranging from 30 to 230 mg/m^2. The mean terminal plasma half-life of ALRT-1057 (1.3 hours) changed very little after several weeks of dosing and peak plasma concentrations equaled or exceeded concentrations that were effective against retinoid-sensitive cells *in vitro*. Despite favorable pharmacokinetics, only one patient achieved CR. Although ALRT-1057 may not induce its own catabolism to the same degree as ATRA, it was still unable to overcome clinically acquired resistance to ATRA in APL (Miller WH Jr, etal, Blood, 1995 Jun 1, 85(11):3021-7).

In phase I/IIa trials conducted at Memorial-Sloan Kettering Cancer Center (NY, NY), oral ALRT-1057, administered at daily doses as high as 230 mg/m^2, exhibited excellent bioavailability with drug plasma levels proportional to the administered dose over a broad range. A topical version of this drug is in phase II trial for the treatment of Kaposi's sarcoma and mycosis fungoides. A phase IIb clinical trial with oral ALRT-1057 in NHL is being conducted at the M. D. Anderson Cancer Center.

Aronex Pharmaceuticals (The Woodlands, TX) is developing Tretinoin^{LF}, an intravenous liposomal formulation of ATRA. Aronex obtained exclusive development and marketing rights to liposome-encapsulated ATRA from M. D. Anderson Cancer Center. The IV liposomal formulation is being developed to sustain therapeutic levels of ATRA in the circulation, not attainable with the oral drug. In a phase I clinical trial, two of five patients with APL, achieved remissions after treatment with Tretinoin^{LF}. Phase I trials also demonstrated that the drug could be safely delivered at doses sufficient to produce activity against APL. In September 1995, Aronex initiated a phase II trial of Tretinoin^{LF} in patients with APL who have relapsed following prior therapy with either oral ATRA or other chemotherapy. The multicenter study, which will enroll 80 patients at 20-30 centers, is designed to assess the utility of the company's agent in inducing and maintaining remission in patients who have relapsed following prior therapy. The product also recently entered phase II/III clinicals in Kaposi's sarcoma in collaboration with Genzyme.

Leo Pharmaceutical Products (Ballerup, Denmark) is preclinically evaluating a vitamin D3 derivative, KH 1060, which is 10 times more potent than 9-*cis*-retinoic acid in inhibiting clonal proliferation of APL (NB4) cells.

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

Incubation of the cells with a combination of KH 1060 and 9-*cis*-retinoic acid decreased expression of apoptosis-suppressor protein bcl-2 from 100% in wild type cells to <2%; expression of apoptosis-promoter protein bax increased after incubation with either KH 1060, 9-cis-RA, or a combination of both, from 50% in controls to 70%, 75% and 90%, respectively Apoptotic death of NB4 cells was observed after incubation with either analog and increased to >50% of cells with the combination. Combining retinoids acting by putatively different mechanisms may prove an effective strategy in the treatment of APL and AML (Elstner E, etal, ASH95, Abs. 1728).

Ligand Pharmaceuticals (San Diego, CA), in addition to its involvement with ALRT, is also pursuing its own in-house development of retinoids. It is currently clinically evaluating LGD-1069 (3-methyl-TTNEB) that binds selectively to RXR and may exhibit a pattern of activity and/or toxicity distinct from other retinoids. The oral formulation of the drug, Targretin Oral, was well tolerated in a phase I trial in 33 patients with various malignancies. Also, according to interim results reported in January 1996 from a phase I/II controlled multicenter trial of Targretin Topical in CTCL or mycosis fungoides, 33% of 27 patients experienced a response.

Structural modifications of LGD-1069 have resulted in the identification of increasingly potent retinoids with >1000-fold selectivity for RXRs. The most potent and selective of the analogs, LG100268, is being used to investigate RXR-dependent biological pathways. Studies indicate that to date induction of programmed cell death and trans-glutaminase in human leukemic myeloid cells is dependent upon activation of RXR-mediated pathways (Boehm MF, etal, Journal of Medicinal Chemistry, 1995 Aug 4, 38(16):3146-55).

Sparta Pharmaceuticals (RTP, NC) received FDA clearance in late 1995 to begin a 30-patient phase I clinical trial with the retinoid compound, RII retinamide, in myelodysplastic syndrome (MDS). In clinical trials conducted in China in over 600 patients, RII retinamide elicited an overall response rate of 68%. Sparta has been granted exclusive worldwide (outside China) rights to the patents from the Institute of Materia Medica (Beijing, China) which has been concentrating on the synthesis and characterization of novel, potentially non-teratogenic retinoid compounds.

Taxanes

Taxanes, evaluated in numerous phase I/II clinical trials, initiated in 1993, in the treatment of hematologic malignancies, did not elicit significant responses. One phase II clinical trial, however, using paclitaxel (Taxol; Bristol-Myers Squibb) as a 3-hour infusion, in conjunction with GM-CSF, in three NHL patients who relapsed after autoBMT, resulted in event-free disease intervals of 9.2, 5.0 and 2.9 months (Goldberg, etal, ASH95, Abs. 3238).

Topoisomerase Inhibitors/ Naturally-derived Alkaloids

Both topoisomerase I and II inhibitors have been tested in hematologic malignancies. Several topoisomerase I inhibitors that block DNA synthesis, are in development (see FO V1 #2/3, p 56; #4, p 111), including various water-soluble and insoluble derivatives of the plant alkaloid camptothecin, administered parenterally or orally. Two water-soluble derivatives, topotecan (SmithKline Beecham) and irinotecan (Yakult Honsha and Pharmacia & Upjohn) are in late stage development for various cancers and another, the totally synthetic camptothecin analog GG-221 (Glaxo Wellcome), is in phase II clinical trials in colon and lung cancer. The potential role of topoisomerase I inhibitors in the treatment of hematologic malignancies has not been established. For instance, although topoisomerase I is elevated in the lymphocytes of chronic lymphocytic leukemia (CLL) patients and exposure of cells from these patients to topotecan *in vitro* at 2 mM resulted in detectable protein-DNA cross-linking, this effect was not seen in 12 CLL patients who received a bolus dose of 2 mg/m^2, and no remissions were noted (O'Brien S, etal, Cancer, 1995 Mar 1, 75(5):1104-8).

Among topoisomerase II inhibitors clinically evaluated in hematologic malignancies is sobuzoxane, an analog of ICRF-159 (MST-16, Perazolin), in development by Zenyaku Kogyo (Tokyo, Japan), under a collaboration with the Institute of Materia Medica (Shanghai, China). The drug is an orally-active bimolane analog that inhibits topoisomerase II without formation of a cleavable DNA-protein complex. Overall response rate in phase II trials was 29.7% in malignant lymphoma and 46.2% in acute adult T cell leukemia; dose-limiting factor was leukopenia (Tsukagoshi, S, Gan To Kagaku Ryoho Japanese J. of Cancer and Chemotherapy, 1994 June, 21(7):1089-97).

Cephalostatins, a group of thirteen marine-derived alkaloids, have shown potent cytotoxic activity at very low concentrations in myeloid leukemia cells. They act by a unique mechanism, possibly related to interaction with endogenous steroid receptors, induce apoptosis and exhibit significantly higher time- and dose-cytotoxicity for malignant myeloid compared to normal marrow progenitor cells (Lilly M and Pettit GR, ASH95, Abs. 2056).

Harringtonine (HT) and homoharringtonine (HHT) are plant alkaloids isolated from the bark of the evergreen tree *Cephalotaxus hainanensis Li* in the 1970s. In preclinical tests one of the mechanisms of these drugs against tumor cells was apoptosis (Li L, etal, Yao Hsueh Hsueh Pao Acta Pharmaceutica Sinica, 1994, 29(9):667-72). Efficacy with HHT was reported in relapsed and de novo AML and in CML. HHT, currently in clinical trials in the USA, is supplied by the National Cancer Institute (NCI; Bethesda, MD) under an agreement with the Institute of Materia Medica of the Chinese Academy of Medical Sciences (Beijing, China).

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

In a phase II trial, HHT was administered at a dose of 5 mg/m^2 by 24-hour continuous infusion daily for 9 days, to 28 patients with MDS (16) and MDS evolving to AML (12). CR was achieved in 7 patients and PR in one patient, for an overall response rate of 28% (8/28). Median duration of CR was 7 months (range 2-10). Significant universal myelosuppression resulted in a high incidence of induction deaths (13/28) due to neutropenia-related infections. HHT given in this dose and schedule demonstrated limited activity in MDS and MDS/AML, and was associated with prolonged pancytopenia and marrow hypoplasia in many patients (Feldman EJ, etal, Leukemia, 1996 Jan, 10(1):40-2). Administration of HHT at a lower dose or in combination with hematopoietic growth factors is associated with significantly lower toxicity. Among 58 evaluable patients with Ph^1+ CML in late chronic phase (time from diagnosis to therapy longer than 12 months) who were treated with a continuous infusion of HHT at a daily dose of 2.5 mg/m^2 for 14 days for remission induction, and for 7 days every month for maintenance, 42 (72%) achieved CR and 9 (16%) PR. Significant myelosuppression occurred in 39% of induction courses and 9% of maintenance courses. Fever or documented infection was present in 26% of induction courses but in only 8% of maintenance courses (O'Brien S, etal, Blood, 1995 Nov 1, 86(9):3322-6). HHT is currently under phase II clinical trials in combination with interferon and cytarabine (ara-C) in CML.

OLIGONUCLEOTIDE-BASED DRUGS

Oligonucleotide-based therapeutics are being developed for both *in vivo* and *ex vivo* applications in hematologic malignancies. In *ex vivo* approaches oligos are used to purge bone marrow for autoBMT. *In vivo* applications of oligos are in very early stages of development. Although elegant in theory, oligonucleotide-based therapy still faces a lot of hurdles regarding uptake, stability and dosing to achieve effectiveness.

Oligonucleotides, however, may play a role in the treatment of most hematologic malignancies associated with identifiable aberrant production of certain proteins. For instance, oligos specific for IL-10, a potent stimulator of growth of neoplastic B lymphocytes, may be effective against CLL. B-1 cells derived from a murine model of CLL produce significantly higher levels of IL-10 mRNA than normal B-1 or B cells. IL-10 may act as an autocrine growth factor for malignant B-1 cells. Adding antisense oligodeoxynucleotides specific for IL-10 mRNA dramatically inhibited growth of leukemic B-1 cells in a time and dose dependent manner but did not affect control cell lines whose growth does not depend on IL-10. Antisense therapy, targeted at the 5' region of the IL-10 mRNA, inhibited malignant B-1 cell proliferation and, also, IL-10 production by malignant B-1 cells. Because endogenous IL-10 gene activation is critical for B-1 cell expansion, inactivation of the endogenous IL-10 gene by antisense rather than extracellular regulation of IL-10 may inhibit malignant growth (Peng B, etal, Leukemia Research, 1995 Mar, 19(3):159-67).

In March 1995, researchers at Kyoto University in Japan announced that they successfully blocked the production of hsp70 in leukemia cells, using antisense RNA. About 80% of malignant cells stopped dividing and underwent apoptosis within 100 hours after introduction of antisense RNA. Expression of hsp70, and also hsp90 and hsp60, is significantly elevated in the circulating cells of patients with AML compared with cells from CML patients and with normal peripheral blood mononuclear cells. Mononuclear cells from leukemic patients exhibit a heterogenous pattern of hsp expression, differing between patients, cells from individual patients, and hsp proteins. It is possible that hsp expression relates to the differentiation state or proliferative potential of these leukemic cells (Chant ID, British Journal of Haematology, 1995 May, 90(1):163-8).

Genta (San Diego, CA), is constructing antisense oligonucleotides (Anticode G3139) targeted against bcl-2 mRNAs in an attempt to reverse the chemoresistance observed in cancer cells with activated bcl-2. These oligonucleotides were found to decrease the level of Bcl-2 in human cultured cells in preclinical studies. In animal models, one of these oligonucleotides was found to inhibit the growth of a drug-resistant human colon tumors in nude mice, while a control oligonucleotide had no effect. Similar studies have also been conducted by Finbarr Cotter, MD, at the Institute of Child Health (London, UK). In these studies, an anti-bcl-2 oligonucleotide was shown to cure lymphoma-like disease induced by the injection of human B cell lymphoma cells in severe combined immunodeficient (SCID) mice (Cotter, FE, etal, Oncogene, 1994 Oct, 9(10):3049-55). In November 1995, Genta initiated a phase I/II clinical trial in patients with drug resistant follicular lymphoma at the Royal Marsden Hospital (London, UK), in collaboration with the Institute of Cancer Research. Chugai Pharmaceutical (Tokyo, Japan) has the option to license worldwide marketing rights to this potential lymphoma therapy if it decides to fund its further development. Genta's other antisense compound, G-1128, failed to show effectiveness in a phase I clinical trial conducted at M. D. Anderson Cancer Center, for *ex vivo* purging of leukemic cells for autoBMT in CML. G-1128 targeted the bcr-abl gene product [bcr-abl results from the t(9;22) abnormality which translocates the breakpoint cluster region (bcr) of chromosome 22 to the abl oncogene of chromosome 9, resulting in Ph^1]. One of the problems of targeting bcr-abl is the fact that most primitive CML cells do not express this protein. A more appropriate target, currently under evaluation may be c-myb protooncogene.

Lynx Therapeutics (Hayward, CA), a private company established in 1992, is developing antisense-based cancer therapies targeting the p53 and myc oncogenes. In 1993, Lynx completed a phase I clinical trial of LR-

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

3523, a 20-mer phosphorothioate oligodeoxynucleotide analog targeting p53 in the treatment of acute AML and MDS. The drug, administered as a 10-day continuous IV infusion (0.05 mg/kg/hr), did not cause any serious toxicity but higher doses will be necessary to investigate efficacy. Lynx is also conducting a phase I dose-escalation study of LR-3001, a 24-mer phosphorothioate antisense to c-myb for treatment of Ph^1+ CML in accelerated phase or blast crisis. This study which uses repeated courses of 7-day IV infusion of this agent, began in December 1994 at the University of Pennsylvania (Philadelphia, PA). LR-3001 was preclinically evaluated in SCID mouse models of human CML and malignant melanoma, and is also under investigation for use with autoBMT in CML. In a phase I clinical trial, begun in May 1994, bone marrow of CML patients not elligible for alloBMT, was purged *ex vivo* with LR-3001 and cryopreserved. This purged marrow was then re-infused into patients who had undergone myoablative therapy. One of four evaluable patients experienced a durable cytogenic response. Lynx is also studying the *in vivo* efficacy of a 26-mer phosphorothioate oligonucleotide targeted against a bcr-abl breakpoint junction for the treatment of CML (Skorski T, etal, PNAS USA, May 1994, Vol. 91, pp. 4504-4508,). These experiments are being extended to include combination therapies with bcr-abl and either conventional drugs or other antisense agents.

RGene Therapeutics (The Woodlands, TX), established in March 1994, is preclinically evaluating RGA-1512, an antisense oligodeoxynucleotide (nucleic acid methylphosphonate) delivered by a liposomal vector, being developed for *ex vivo* (bone marrow purging) and *in vivo* Ph^1+ CML therapy. In *in vitro* studies, RGA-1512 inhibited growth of CML cells. RGene has exclusive rights to RGA-1512, based on work by collaborators at the M. D. Anderson Cancer Center/University of Texas, the University of Pittsburgh, the University of Tennessee (Memphis, TN) and Aronex Pharmaceuticals. RGene has also secured, via an agreement with Aronex Pharmaceuticals, exclusive worldwide rights to the University of Tennessee's patented cationic liposomes for all applications in cancer and sepsis-related infectious disease. RGene is developing both lipid and non-lipid based delivery systems for *in vivo* gene therapies.

OTHER AGENTS

AntiCancer (San Diego, CA) is developing ONCase (AC9301; Methionase), a drug that targets a metabolic defect found in tumor but not normal cells (also see FO, V1 #1, pp 18 & 19). AntiCancer reported that recent *in vitro* screening of the NCI's organ specific human tumor cell line collection has suggested that ONCase may be applicable to all tumors, including hematologic malignancies. As of late 1995, ONCase was in phase I clinical trials. In treated patients, the level of methioninase declined from 100 mM to 10 mM without any toxic effects noted. In late 1995 AntiCancer entered into an agreement granting Shionogi (Osaka, Japan) the rights to co-develop and exclusively market ONCase in Japan but retained the remaining worldwide rights.

BioCryst Pharmaceuticals (Birmingham, AL) is evaluating topical BCX-34, a small molecule inhibitor of purine nucleoside phosphorylase (PNP), in the treatment of CTCL. BCX-34 was granted orphan drug status in October 1993. In September 1995, the company announced favorable results from a completed 6-month open-label phase II clinical trial of BCX-34. Among 24 patients with stage I/IIA CTCL, seven patients achieved CR, two were clinically free of disease and nine achieved PR for an overall response rate of 18 (75%). The study, being conducted at the University of Alabama and Washington University (St. Louis, MO), was extended for another six months to treat 13 additional patients. A double-blind, randomized, placebo-controlled multicenter phase III clinical trial with a 1% drug concentration of BCX-34 for the treatment of 90 early-stage CTCL patients, was also initiated in late 1995. BioCryst is also evaluating an oral formulation of BCX-34 or the treatment of CTCL and T cell leukemia. In a phase I clinical trial involving three patients with stage IB and IIB CTCL, who were administered both oral and IV formulations, the oral drug demonstrated bioavailability in excess of 76%. Phase I/II clinical trials with this agent began in January 1996.

DepoTech (La Jolla, CA) is developing DepoCyt, a proprietary DepoFoam formulation of ara-C. Interim results, announced in August 1995, based on 32 evaluable patients with neoplastic meningitis arising from solid tumor metastasis participating in a phase III clinical trial, which began in April 1994, showed increased response rate and extended survival times for DepoCyt versus standard therapy (MTX). Neoplastic meningitis is a form of cancer metastatic to the meninges (the soft tissue surrounding the brain and spinal cord) arising from primary cancers. DepoCyt is being developed in collaboration with Chiron (Emeryville, CA).

Mitotix (Cambridge, MA) is developing small molecular weight inhibitors of cyclin-dependent kinases (cdks), a family of enzymes that coordinate the cell division cycle, that may prove useful in the treatment of lymphoma. Periodic activation of cdks requires their association with proteins called cyclins, and is also controlled by post-translational modifications (phosphorylation/dephosphorylation) and by naturally occurring cdk inhibitors. Alterations of cdk pathways have been shown to correlate with cell proliferation associated with cancer. Cdk inhibitors are expected to selectively block this proliferation of cancer cells. The company's initial lead program focuses on cdk4/cyclin D1 whose alterations have been observed in many cancers. Cyclin D1, itself the product of an oncogene, is overexpressed in esophageal, breast, and colon cancers and lymphomas. Mitotix is using screening procedures to identify small

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

molecule compounds that selectively inhibit the cdk4/cyclin D1 complex by mimicking the function of certain oncogenes, or by directly blocking the active site of the enzyme. The company is using structure based drug design and combinatorial chemistry to construct potential lead candidates. In late 1995, Mitotix entered into a collaborative agreement with DuPont Merck Pharmaceuticals (Wilmington, DE) to develop and commercialize various cdk inhibitors, under development by Mitotix including cdk4/cyclin D1 inhibitors, and new agents identified using DuPont Merck's compound library, for the treatment of cancer. Under the terms of the agreement, DuPont Merck made an initial payment of $17 million and may invest a total of $55 million, in the form of equity and milestone payments. Mitotix will also receive royalties on worldwide product sales. In exchange, DuPont Merck obtained exclusive worldwide rights to commercialize cdk-based therapeutics and radiopharmaceutical diagnostics. Mitotix retains the rights to certain cdk targets for non-cancer indications and to development of gene therapy and/or antisense approaches using such targets. Mitotix also retains rights to certain diagnostic applications (oncogene typing) and has an option to co-promote, in the USA, any agents resulting from the collaboration. Agents included in the agreement, in addition to inhibitors of cyclin D1, are inhibitors of cyclin E, and mimetics of tumor suppressor gene, pl6, present in many solid tumors. Mitotix obtained exclusive rights to cyclin D1 and p16 from Cold Spring Harbor Laboratory (Cold Spring Harbor, NY) and exclusive rights to cyclin D1 patent applications from Massachusetts General Hospital (Boston, MA). In a separate agreement, Mitotix and DuPont Merck will also co-operate in a research project to develop inhibitors of the ubiquitin-mediated degradation of p53, as anticancer agents.

MEETING COVERAGE

ADVANCES IN BREAST CANCER TREATMENT

A REPORT FROM THE SIXTH INTERNATIONAL CONGRESS ON ANTI-CANCER TREATMENT (ICAT), PARIS, FRANCE, FEBRUARY 6-9, 1996

DETECTION OF ANGIOGENESIS

Angiogenic activity appears to be a prognostic factor in early-stage breast cancer. Although early-stage breast cancer has a better prognosis in the absence of node involvement, 30% of node-negative patients will die of their disease. Well-established factors such as tumor size, histoprognostic grade, and negative hormone receptor status, may help identify women with poor prognosis who may benefit from adjuvant therapy. However, even with adjuvant therapy, some patients relapse. Since angiogenesis is necessary for tumor growth, tumor microvessel count (TMC) is becoming a new indicator for node-negative breast cancers and may predict their clinical outcome. Methodology to carry out TMC is delineated in Exhibit 3.

To test this hypothesis, tumor angiogenic activity was evaluated in 255 node-negative breast cancer patients who underwent surgery between 1979 and 1994 and who did not receive adjuvant therapy. Mean age of these women was 59 years; 24% were premenopausal; tumor size was greater than 2.0 cm in a third of the patients, and receptor status was ER+ PR+ (57%), ER- PR- (11%), ER+ PR- or ER- PR+ (32%). Within a median follow-up of 157 months, there were 86 relapses (32 metastases, 32 local relapses and 22 local plus distant relapses) and 41 deaths. Mean TMC was 94 and median TMC was 86; the range was between 28 and 348. Patients whose tumors had fewer than 69 microvessels achieved statistically significant longer disease-free intervals, but their survival curves were not different. Use of TMC may be of considerable value in helping select patients who may respond to angiogenesis inhibition (Namer M, etal, Abstracts of the 6th ICAT, Pg 68:#110).

Parvis Gamagami, MD, and associates at the Breast Center (Van Nuys, CA) demonstrated, based on a retrospective review of mammograms performed up to 13 years before cancer was diagnosed, that angiogenesis proceeded 90% of nonpalpable and 100% of palpable breast lesions. Also, it appears that tumor angiogenesis gives rise to hot spots in the breast before any signs of cancer are present. This observation may resurrect the application of thermography in breast cancer diagnosis and screening. Dr. Gamagami's group is currently evaluating thermography as a guide for biopsy. Angiogenesis as a diagnostic or disease monitoring approach is still in its infancy and rather controversial. For a comprehensive review of angiogenesis in cancer diagnosis and therapy, including an exhaustive database of angiogenesis inhibitors under development, see FO, V1 #7/8, pp 185-199.

CHEMOTHERAPY

Primary Medical Treatment of Operable Breast Cancer

Primary medical treatment offers good local and systemic control of operable breast cancer. Furthermore, decrease in tumor size, both in the breast and in the nodes, may obviate surgery in about one third of treated patients. If, and when, surgery is required, tumor excision is possible most of the time, allowing a non-mutilating approach to be used in up to 90% of these women, even for some tumors not completely sterilized by chemotherapy or others initially greater than 5.0 cm in diameter.

Over a four-year period, among 258 women with mainly T2 and T3 breast cancers treated by a chemotherapy regimen incorporating doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) for at least

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

Exhibit 2
Novel Agents in Development for the Treatment of Hematologic Malignancies

Primary Developer/ Affiliate(s)	Generic Name/ Number/Brand Name	Drug Type/Target/ Mechanism/Delivery	Status/Location/ Indication/	Comments
	Trimidox (3,4,5-trihydroxy-benzohydroxamidoxime)	Inhibitor of ribonucleotide reductase (RR), an enzyme linked with malignant transform-ation and tumor cell growth	Preclin/Europe/ APL	Szekeres T, etal, Blood, 1994 Dec 15, 84(12):4316-21
Allergan Ligand Retinoid Therapeutics (ALRT)	9-*cis*-retinoic acid/ ALRT-1057, LG-1057, LGN-1057, LGD-1057	Chemically synthesized retinoid analog/binds to both retinoic acid receptors (RARs) and retinoid "X" receptors (RXRs)/ inhibits cell proliferation and induces apoptosis and cell differentiation/PO	Phase IIb (9/95)/USA/ APL	Also topical formulations for CTCL; LGD-1057 analogs are also being developed
American Home Products (Lederle)	Enloplatin/CL-287110	"3rd generation" platinum complex	Phase I/USA/ leukemia, lymphoma	
Amgen (Synergen)	Anakinra, interleukin-1 receptor antagonist (IL-1ra or IRAP)/Antril	Recombinant non-glycosylated IL-1receptor antagonist expressed in *E. coli*/ competitively inhibits the biological activities of IL-1	Phase I/II/USA/CML	
AntiCancer/Shionogi (Japan)	ONCase/AC9301/ Methionase	Targets a metabolic defect found in tumors but not normal cells	May have application in hematologic malignancies	Phase I clinical trials (10/95)/USA
Apollon	Genevax	Naked DNA gene tranfer/ bacterial plasmid containing encoding DNA sequences/ intramuscular injection	Phase I/USA/ T cell lymphoma	
Aronex Pharmaceuticals/ M. D. Anderson Cancer Center (licensor)	All-trans retinoic acid, (ATRA)/AR-623/Tretinoin	Retinoid/liposomal formulation/IV	Phase II (9/95)/ USA/APL	Also in phase II/III in Kaposi's sarcoma in collaboration with Genzyme
BioCryst Pharmaceuticals	BCX-34	Small-molecule inhibitor of purine nucleoside phosphorylase (PNP)/PO	Phase I/II(1/96)/USA/ T cell leukemia	A topical formulation (orphan drug) is in phase III (9/95) clinical trials for CTCL
Bristol-Myers Squibb	Etopophos, etoposide phosphate/BMY-40481	Water-soluble prodrug of etoposide/PO		NDA 6/94/USA nscl and other cancers; more soluble; less preparation is needed for dosing (see FO,V1 #4)
Byk Gulden	Dexniguldipine/ B859-035, B895-35	R-enantiomer of the calcium antagonist niguldipine/Ca2+ entry blocker, inhibits calmodulin and PKC; potent modulator of P-gp multidrug resistance/PO	Phase II/Germany/ MDS, AML, CML, multiple myeloma	Also see FO,V1 #5, p 129
Celltech/ American Home Products (American Cyanamid)	CCP-771, anti-CD33 MAb	rhMAb linked to calichaemicin/ binds to CD33, a specific antigen present on myeloid progenitor cells/IV	Phase I/II (6/95)/USA/AML	
Coulter	Anti-B1 MAb conjugated to ^{131}I	MAb-^{131}I radioimmunocnjugate/ directed against CD20/IV	Phase III/USA/B cell lymphoma; phase II/ USA/B cell lymphoma in conjunction with BMT	

— *continued on next page*

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

CytRx/ Rush-Presbyterian St. Luke's Hospital	Cremophor EL/CRL-1336, CRL-1337	Solubilizing agent; chemosensitizer/reversible inhibitor of P-gp/IV	Phase I (b10/94)/ USA/relapsed or refractory acute leukemia, multiple myeloma	Also see FO,V1 #5, p 129
DepoTech/ Chiron	Cytarabine (ara-C) formulation/DTC-101/ DepoCyt	DepoFoam formulation of cytarabine/intra-CSF	Phase III/USA (b3/94); Canada (b10/94)/ meningeal leukemia	
Eisai	E-7010	Sulfonamide/inhibits tubulin polymerization/PO, IV, IP	Phase I/Japan	
Genta	Anticode G3139	Antisense oligonucleotide/binds to mRNA of bcl-2 and down-regulates production of BCL-2; induces apoptosis/IV	Phase I (b11/95)/ UK/follicular NHL	Chugai has option to license worldwide marketing rights
Genta/M. D. Anderson Cancer Center	Anticode oligonucleotides, anti-bcr-abl/G-1128	Oligonucleotide/binds to mRNA produced by the aberrant Ph^1 chromosome and prevents cell proliferation/*ex vivo*	Phase I/II/USA/CML	In combination with chemotherapy; Chugai has option to license worldwide marketing rights
Glaxo Wellcome/ Cambridge U (UK; developer); BTG (licensor)	Campath-1H	Humanized MAb/binds to CDW52 on lymphocytes/ causes cell lysis	Phase II (discontinued 9/94)/ CLL	
Glaxo Wellcome/ Cancer Research Campaign	1069C85	Synthetic tubulin binder/inhibits microtubule activity/IV, PO	Phase I/II/USA/NHL	
Hoechst Marion Roussel	28,314		Phase I/II/USA/ leukemia	
Ibex (Continental Pharma Cryosan)/ McGill U		Oral delivery of enzyme-based therapeutics/treatment adjuvant	Research/Canada/ ALL	
ICN Pharmaceuticals/ U Indiana Medical School, M. D. Anderson Cancer Center, NCI (NIH), Warner-Lambert	Tiazofurin riboxamide, TCAR, tiazol/CI-909, CPD-5825, ICN-4221, NSC-286193/Tiazole	Inosine monophosphate dehydrogenase inhibitor/depletes metabolites of the guanylate biosynthetic pathway/IV	Phase III/USA/ leukemia	Responses observed in blast cells of treated patients include chemotherapy, induced differentiation, and down-regulation of c-Ki-ras and c-myc oncogenes (Weber G, etal, Pharmacy World and Science, 1994 Apr 15, 16(2): 77-83)
IDEC Pharmaceuticals/ Genentech (ww rights abroad, co-promote in USA)	IDEC-C2B8 MAb; pan B MAb	Anti-lymphoma chimeric MAb/ targets CD20 antigen expressed on mature and malignant B cells/ depletes such cells, binds complement and effects ADCC/IV	Phase III/USA (b4/95)/B cell NHL (low-gradeand follicular); preclin/ USA/CLL	
IDEC Pharmaceuticals	IDEC-Y2B8 yttrium conjugate	Anti-CD20 MAb coupled to ^{90}Y	Phase I/USA/ B cell NHL	Genentech has option
Ilex Oncology	Aminopterin (AMT)	Purified and reformulated AMT	Phase I (3/96)/ USA/refractory childhood AML	
Ilex Oncology/Sanofi (ww marketing rights)	Mitoguazone	Polyamine biosynthesis inhibitor	Phase II/USA/refractory/relapsed AIDS-related lymphoma	Orphan drug

— *continued on next page*

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

ImmunoGen/ Dana-Farber Cancer Institute	Oncolysin CD6, anti-CD6,-bR, anti-T12-bR	Conjugate of blocked ricin and a MAb/targets T cell subset responsible for T cell malignancies and acute organ transplant rejection	Phase I/II/USA T cell malignancies	On hold as of 1/96
ImmunoGen/ Dana-Farber Cancer Institute	Oncolysin M, anti-CD33-bR, anti-My9-bR	Conjugate of blocked ricin and a MAb/targets My9 epitope of the myeloid stem cell, and all cells derived from it except RBCs/*ex vivo*	Phase II/USA; phase I/II/Canada/ CML	Phase II completed as of 1/96; on hold
ImmunoGen/ Dana-Farber Cancer Center	Oncolysin M	Anti-My9 MAb linked to blocked ricin/*ex vivo*	Phase II (c/95)/USA/ *ex vivo* bone marrow purging in AML	No further development reported
ImmunoGen/ Dana-Farber Cancer Institute, Roussel-Uclaf, NCI (NIH)	Oncolysin B, anti-B4-bR, anti-CD19-bR	Anti-B4 MAb linked to blocked ricin	Phase III/USA (b93), Canada/post-autoBMT leukemia and NHL; phase I/II (b 9/94)/USA/in combination with chemotherapy and in *ex vivo* bone marrow purging; phase II (c 9/95)/USA/AIDS-related lymphoma	
ImmunoGen	Anti-B4-DC1	Small drug immunoconjugate/ DC1 linked to anti-B4 MAb	IND (as of 1/96)/USA/ relapsed lymphoma	
Immunomedics	ImmuRAIT LL2	Murine MAb LL2 conjugated to ^{131}I	Phase I/II/USA	Being replaced by humanized version
Immunomedics	Hummanized-LL2	Hummanized MAb LL2 conjugated to ^{131}I	Preclin/USA/ B cell lymphoma	
Immunomedics	Hummanized-LL2	Hummanized MAb LL2 conjugated to ^{90}Y	Preclin/USA/ B cell lymphoma	
Immunomedics	Dox-LL2	Hummanized MAb LL2 conjugated to doxorubicin	Research/USA/ B cell lymphoma	
InflaZyme Pharmaceuticals		Phosphonate/inhibits signal transduction pathways involved in cancer cell growth and differentiation	Research/Canada/ leukemia, lymphoma	Awarded a USA patent in late 1994
Innovir/Yale U	External guide sequences (EGS)	Small, modified, stabilized RNA molecule (short oligos) engineered to bind to disease-associated RNA to create a structure of RNA naturally cleaved by ribozyme RNase P	Preclin/USA/APL	
Johnson & Johnson (R.W. Johnson Pharmaceutical Research Institute)	Loxoribine/RWJ-21757	Di-substituted guanine ribonucleoside/potent immunostimulant; enhances natural killer cell activity, B lymphocyte proliferation and antibody synthesis	Preclin/USA/B-CLL	
Kyowa Hakko/NCI	UCN-01, 7-hydroxy-staurosporine, UCN-02	Natural product isolated from *Streptomyces sp N-126*/PKC inhibitor	Preclin/USA/CLL	
Leo Pharmaceutical Products	KH 1060	Retinoid, vitamin D3 analog	Preclin/USA/ APL and AML	
Ligand Pharmaceuticals	3-methyl-TTNEB/ LGD-1069/Targretin Oral	Retinoid/binds selectively to RXR/PO	Phase I/USA/ various malignancies	

— *continued on next page*

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

Lynx Therapeutics	LR-3001	24-mer phosporothioate antisense oligonucleotide/ inhibits c-myc	Phase I/USA/CML in accelerated phase or blast crisis	
Lynx Therapeutics		26-mer phosporothioate antisense oligonucleotide/inhibits bcr-abl	Research/USA/CML	
Lynx Therapeutics	LR-3523	20-mer phosphorothioate oligodeoxynucleotide analog/ targets p53	Phase I (c)/USA/ AML and MDS	
Medarex/Dartmouth U (licensor)	MDX-11, PM-81,	Bispecific MAb/binds to leukemia cells; triggers the complement system	Phase I/II/USA/AML	
Medarex/Dartmouth U (licensor)	MDX-22	Bispecific MAb/bone marrow purging/*ex vivo*	Phase II (investigator-sponsored IND)/USA	Orphan drug
Mercian/Roger Bellon (Rhône-Poulenc Rorer), Yamanouchi, Behringerke (Hoechst), Lundbeck, Almirall, Zuellig, Dong-A	Aclarubicin, aclaciomycin-A/ NSC-208734, Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anthracycline antibiotic	L/outside the USA/ various cancers	A license to Bristol-Myers Squibb for N. and S. America was discontinued; effective salvage regimen for daunorubicin-resistant ANLL in children (Nibu K, etal, Pediatric Hematology and Oncology, 1995 May-Jun, 12(3):251-8)
Milkhaus Laboratory	LDI-200	Formulation of chorionic gonadotropin	Phase I/II/USA/ leukemia	
Mitotix/DuPont Merck Pharmaceuticals	Cyclin D1 inhibitor	Small molecules/cyclin-dependent kinase (cdk)4/cyclin D1 inhibitor	Preclin/USA/NHL	
Mitsui Pharmaceuticals/ BASF (Knoll)	MS-209	Quinilone derivative/ chemosensitizer; inhibits P-gp/PO	Phase II/ Japan/leukemia	
Novartis (Ciba Pharmaceuticals)	CGP 57148	2-phenylaminopyridine derivative/ inhibits abl and platelet-derived growth factor (PDGF) receptor protein-tyrosine kinases	Preclin/USA/CML	
NCI (NIH)/Institute of Materia Medica (China; supplier)	Homoharringtonine (HHT), harringtonine (HT)	Natural product isolated from the bark of the evergreen *Cephalotaxus hainanensis Li*; alkaloid/inter-nucleosomal DNA degradation	Phase III/Italy, China; phase II/USA/MDS, AML, CML	
NCI (NIH)/ Pharmachemie	Decitabine, dezocitidine/ NSC-127716, DAC	Antimetabolite/DNA synthesis inhibitor/IV infusion	Phase II/USA, Europe/leukemia	
Pharmacia & Upjohn (NA licensee)/Yakult Honsha and Daiichi Pharmaceutical (co-developers)	Irinotecan/CPT-11/ Camptosar	Topoisomerase I inhibitor/IV	May have application in NHL	NDA (10/95)/USA/ colon cancer; oral formulation also in development
Pharmacia & Upjohn/ Taiho, NCI (NIH)	Menogaril, menogarol, methylnogarol/7-OMEN, NSC-269148, U-52047, TUT-7/Tomosar	Nogalamycin derivative, antibiotic/DNA antagonist/PO, IV		Phase III/USA in various solid tumors; may have utility in adult T cell leukemia (Hata H, etal, Gan To Kagaku Ryoho Jap J of Cancer and Chemotherapy, 1995 Jul, 22(8):1057-61)

— *continued on next page*

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

Pharmacia & Upjohn/ Yakult Honsha (Japanese co-development and co-marketing rights), EORTC	Adozelesin, adezolin/ U-73975/Adosar	Bifunctional analog of cyclopropylpyrrolo-indole antitumor antibiotics CC-1065/non-intercalative binding in the minor groove of double-stranded DNA (ds-DNA) at A-T-rich sequences followed by covalent binding with N-3 of adenine in preferred sequences/IV	Phase II (9/95)/ USA; phase I (9/94)/ Japan	In a phase I trial adozelesin was administered to 29 patients as a 24-hour continuous IV infusion, initially every 3 weeks, changed to every 6 weeks (recommended dose is 100 mcg/m^2) because of myelosuppression; no antitumor responses were observed (Fleming GF, etal, J NCI, 1994 Mar 2, 86(5):368-72); also see FO,V1 #4
Pharmacia & Upjohn/ NCI (NIH), EORTC	Bizelesin/NSC-615291, U-77779	Bifunctional analog of adozelesin; highly potent bis-alkylating anti-tumor agent/binds to and alkylates DNA at the N-3 position of adenine in a sequence-selective manner/ IV, IP	Phase I/II (9/95)/USA	Bizelesin is stable in organic solvents but less stable in aqueous solutions
Pharmacia & Upjohn/ NCI(NIH), EORTC	Carzelesin/NSC-D-619020, U-80244	Cyclopropylpyrrolo-indole prodrug containing a relatively nonreactive chloromethyl precursor to the cyclopropyl function/action similar to bizelesin and adozelesin/IV	Phase I/II (9/95)/ USA	
Pharmacia & Upjohn	Roquinimex/LS-2616/ Linomide	Immunomodulator/PO	Phase III/USA/ leukemia patients treated with autoBMT	Phase II/Europe/ kidney cancer, malignant melanoma
Pharmacia & Upjohn	Tallimustine/FCE 24517	Alkylating benzoyl mustard derivative/sequence-specific DNA, minor groove binder (MGB) of B-DNA	Phase I/II (9/95)/USA	
Pharmacia & Upjohn	Bropirimine/Remisar	Immunomodulator/PO	Phase III/USA (9/94); phase II/Japan/ refractory NHL	
PharmaMar	Ecteinascidins/ET-743, ET-722, ET-736, ET-745, ET7	Marine product derived from the Caribbean tunicate *Ecteinascidia turbinata*/may form covalent adducts to DNA	Preclin/Spain/NHL	
Protein Design Labs/ Kanebo (licensee, Asia)	HuM195/SMART M195	Humanized anti-CD33 MAb/ reduces or eliminates residual disease by ADCC	Phase II/III/USA (6/94); phase I (9/95) Japan/AML	
Research Corporation Technologies/ Boston U	IL-16 (formerly lymphocyte chemoattractant factor, or LCF)	IL-16 antagonists/may block proliferation of CD4+ T cells	Research/USA/ T cell lymphoma	
RGene Therapeutics	RGA-1512	Antisense oligonucleotide/ targets an oncogene on the Ph^1 chromosome/liposomal vector, *ex vivo* and *in vivo*	Preclin/USA/CML	
Sankyo	RKS-1286, CNDAC	Nucleoside/ DNA-strand-breaking	Preclin/Japan/ leukemia	

— *continued on next page*

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

Sanofi (was in development by Sterling Drug)	Hepsulfam/NSC-329680	Bisulfamic ester, structurally similar to busulfan/bifunctional alkylator inducing both DNA-DNA and DNA-protein crosslinks/IV	Phase I/USA/ advanced refractory leukemia	Recommended phase II dose of 480 mg/m^2 as a single 2-hour IV infusion provided relatively little clinical benefit; dose-limiting toxicity is CNS-related; hematopoietic support may be necessary at doses exceeding 800 mg/m^2 (Larson RA, etal, Cancer Chemotherapy and Pharmacology, 1995, 36(3): 204-10)
Schering-Plough	IL-10	Cytokine/promotes apoptosis	Phase I/II/USA/CLL	
Seragen	Interleukin-4 fusion toxin, IL-4 fusion toxin/ DAB_{389}IL-4	IL-4 fusion toxin/fused with fragments of diphtheria toxin	Preclin/USA/leukemia, lymphoma, IL-4 receptor-expressing malignancies	*In vitro*, the toxin selectively bound and killed malignant cells
Seragen	Interleukin-6 fusion toxin, IL-6 fusion toxin/DAB_{389}IL-6	IL-6 fusion toxin	Preclin/USA/ multiple myeloma	
Seragen/Eli Lilly, Ajinomoto	Interleukin-2 fusion toxin, IL-2 fusion toxin/ DAB_{389}IL-2, DAB486IL-2	Fusion toxin/ interleukin-2 receptor	Phase III/USA/CTCL; phase II/USA/NHL	Seragen obtained worldwide rights from Ajinomoto to certain IL-2 gene patents
SmithKline Beecham	Topotecan, hycaptamine/ NSC-609699, SK&F-104864	Topoisomerase I inhibitor/ IV, PO	Clinical/USA/ ALL, CML	
Sparta Pharmaceuticals/ Institute of Materia Medica (licensee)	RII retinamide	Retinoid	Phase I (b1/96)/ USA/MDS	
Stanford U	Tumor specific idiotype vaccine	Composed of tumor idiospecific protein conjugated to a carrier and mixed with an immunologic adjuvant	Phase I/II(b88)/USA/ B cell (advanced follicular) lymphoma	
Sugen	ALL-TK antagonists	ALL-TK antagonist/inhibits growth of human leukemic cells	Preclin/ USA	
Sugen	ALL-TK antagonists	Small molecule/antagonist of tyrosine kinase (TK) activity/ inhibits growth of human leukemic cells	Preclin/ USA/ALL	
Sugen	GRB2 antagonist	Small molecule/growth factor receptor binding protein 2 (GRB2) antagonist	Research/USA/CML	Binding of GRB2 to bcr-abl and TK is an essential step in the formation of bcr-abl-induced cancers
Sunkyong Industries	SKI-2053R	Alkylating agent, platinum-based drug/IV	Phase I/S. Korea/ leukemia	
Tanox/Takara Schuzo	Migis antibodies, migis-IgA	MAbs/inhibits IgA synthesis, preventing glomerular deposition of IgA immune complexes	Preclin/lymphoma, leukemia	
Techniclone/Alpha Therapeutic (Green Cross licensee in NA, Asia and certain parts of Europe); Biotechnology Development (licensee; elsewhere)	^{131}I-Lym-1, Lym-1/Oncolym	MAb conjugated to iodine-131 (^{131}I)	Phase III (1/96)/ USA/B cell NHL	Orphan drug

— *continued on next page*

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

Triangle Pharmaceuticals		Small molecules	Preclin/USA/leukemia and lymphoma	The company is negotiating licenses in this area
U Minnesota	Conjugate of genistein and MAb B43	Immunoconjugate/targets the CD19 molecule expressed on B cell precursor leukemia (BCPL)	Preclin/USA/BCPL	
U Wisconsin	Perillyl alcohol (POH)	Cyclic monoterpene/inhibit isoprenylation of small G proteins; inhibit farnesyl transferase; induces apoptosis	Phase I	ASH95 Abs. 654
Vical	Allovectin-7	Vaccine (gene transfer)/encodes a foreign tissue antigen (HLA-B7)/intratumoral injection	Phase II (b9/95)/ USA/NHL	
Vical	Leuvectin	Gene therapy/IL-2 gene in a plasmid-lipid complex/ intratumoral injection	Phase I/II (b4/95)/ USA/ lymphoma	
Wyeth-Ayerst	CMA-676		Clinical/relapsed AML (9/95)	
Yeda	Vitamin D3-derivative	Inhibits cell growth and proliferation	Preclin/Israel	

four cycles (up to six cycles if the tumor continued to respond), at three week intervals [tamoxifen (10 mg twice daily) was also administered to hormone-dependent patients], a very high response rate was seen with an acceptable low toxicity. The response rate included 13% CR and 70% PR [25% of almost complete responses (ACR) with minimal residual disease and 45% with a substantial amount of residual disease]. Stable disease was observed in 16% of patients, and disease progressed in 1%.

Radiotherapy was started two to three weeks after CR or ACR. No surgery was needed in 38% of cases. For those with stable disease or PR (62%), tumor excision was the second line of treatment. Axillary dissection was not performed unless suspicious nodes were still palpable. Surgical patients were also treated by post-operative radiotherapy with concomitant chemotherapy in larger tumors. Only 23 total mastectomies were required. With an average follow-up of 30 months, a wide local excision was needed in 18 patients because of local recurrence, or non-sterilization in 14 patients with ACRs. There were 33 distant metastases and 22 deaths due to generalization of the disease in the total study group (Poisson R, etal, Abstracts of the 6th ICAT, Pg 70:#117).

Monotherapy

S-1, a new oral antitumor agent, appears to offer promising therapeutic benefits in patients with advanced breast cancer. This newly developed drug biochemically modulates 5-fluorouracil (5-FU), inhibiting its degradation in the liver and phosphorylation in the digestive tract. To accomplish this, tegafur (FT), 5-chelo-2,4-dihydroxypyridine (CDHP), and potassium oxonate (OXO) were combined in a molar ratio of FT:CDHP:OXO=1:0.4:1. FT releases 5-FU continuously in the liver, CDHP inhibits degradation, and OXO inhibits phosphorylation. UFT, a fixed-ratio combination of uracil and tegafur (Ftorafur; Taiho), a prodrug that is absorbed orally and metabolized *in vivo* to 5-FU, is one of the leading anticancers in Japan (see FO V1, #2/3 p 55).

In phase I studies, using a single 28-day consecutive administration in 17 evaluable patients with a variety of solid tumors, MTD was estimated at 150-199 mg/body/day, once-a-day, or 75-99 mg/body/day, as a twice-a-day regimen. A number of early phase II studies were carried out administering S-1 to patients with a wide range of solid tumors. In the study on advanced breast cancer, in 27 evaluable women, the overall objective response rate was 40%, with four CRs and 17 PRs. Major toxicities (over grade 3), observed in patients with advanced breast cancer who received S-1, were hemoglobinemia (3.7%) and stomatitis (3.7%). Based on these findings, plus those carried out in patients with gastric, colorectal and head and neck cancer, further studies with S-1 are merited in persons with advanced cancer (Taguchi T, Abstracts of the 6th ICAT, Pg 58:#73).

Combination Therapy

Docetaxel (Taxotere; Rhône-Poulenc Rorer), combined with vinorelbine, is very active against metastatic breast cancer. In a phase I dose-ranging study, 28 women with metastatic breast cancer, previously untreated with chemotherapy, received vinorelbine (20 to 22.5 mg/m^2 by 30 minute iv infusion on days one and five), followed by docetaxel (60-100 mg/m^2 by one-hour IV infusion on day one only), repeated every three weeks. Five different dose levels were administered to at least three patients

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

per dose level. Patients were also premedicated with dexamethasone, antihistamines, and ranitidine to mitigate potential drug-related adverse effects.

Two MTDs were reached. At 75 mg/m^2 docetaxel plus 22.5 mg/m^2 vinorelbine, dose-limiting toxicities were febrile neutropenia and mucositis. On the assumption that mucositis was more related to vinorelbine than docetaxel, a lower dose of vinorelbine (20 mg/m^2) was investigated with increasing doses of docetaxel. This protocol reached a second MTD at 20 mg/m^2 vinorelbine plus 100 mg/m^2 docetaxel. The recommended dose for phase II studies is 85 mg/m^2 docetaxel on day one and 20 mg/m^2 vinorelbine on days one and five. The overall objective response rate was 70%. Responses were seen at every level but more so at levels four (V 20 mg/m^2 D 85 mg/m^2) and five (V 20 mg/m^2 and D 100 mg/m2) (Fumoleau P, etal, Abstracts of the 6th ICAT, Pg 65:#97).

Exhibit 3
Method of Counting Microvessels

- Select a representative histologic sample, and cut 5 m-thick sections from the paraffin-imbedded specimen
- Immunostain the sections with an endothelial marker to highlight microvessels (venules and capillaries)
- Manually scan the immunostained section at low magnification (40-100x) to identify areas of tumor with the greatest number of highlighted microvessels ("hot spots")
- Count all vessels at 200x field (0.74 mm^2 area) within the hot spot; endothelial clusters should be counted as a single microvessel; presence of a lumen is not necessary for a structure to be counted as a microvessel

Note: Each evaluation should be performed by two investigators using a double-headed microscope; each investigator should agree on what is an identifiable microvessel

Source: Vincent W. Li, the Angiogenesis Foundation

Paclitaxel (Taxol; Bristol-Myers Squibb), in combination with vinorelbine, is an effective salvage regimen in women with advanced breast cancer. Combination therapy with paclitaxel (135 mg/m^2), administered as a three-hour IV infusion, plus vinorelbine (25 mg/m^2 on days one and three or eight) may be administered at greater dose intensity on a day one and three schedule. Among 34 previously treated patients (all but two were exposed to anthracyclines) with advanced breast cancer, 35% experienced an objective response. Side effects of the drug combination included grade 4 neutropenia, observed in 63% of courses, with 14 episodes of febrile neutropenia. Also, grade 3 mucositis was reported in the vinorelbine days one and three arm (Conte PF, etal, Abstracts of the 6th ICAT, Pg 148:#S17).

Paclitaxel, given as a three-hour infusion, in combination with doxorubicin, is a highly active, but also toxic, (particularly cardiotoxic), regimen in metastatic breast cancer. In a phase I/II study, 29 women with metastatic breast cancer who was treated at most with one prior adjuvant chemotherapy regimen, were given doxorubicin as a 30-minute infusion, followed by paclitaxel as a three-hour infusion every three weeks at dose levels of 50/155 mg/m^2 (3 patients), 60/175 mg/m^2 (21 patients) and, 60/200 mg/m^2 (5 patients). Eighty-three percent of patients had bone and/or visceral metastases. In 29 evaluable patients, overall response rate was 83%, with seven CRs and 17 PRs. Median time to progression was nine months; nine patients progressed during therapy, four in the central nervous system. Main toxicities, among 265 courses of chemotherapy, included neutropenia, paresthesias, nausea and vomiting, alopecia, myalgia, and cardiotoxicity [50% of patients experienced a drop in left ventricular ejection fraction (LVEF) to below normal levels and six developed heart failure]. Consequently, doxorubicin at a cumulative dose of 360 mg/m^2 was stopped (Gehl J, etal, Abstracts of the 6th ICAT, Pg 148:S16).

Vinorelbine (Navelbine; Glaxo Wellcome), in combination with mitoxantrone and carboplatin, proved a safe, well tolerated, and effective first line treatment in metastatic breast cancer, both in patients with a favorable prognosis (one metastatic site) and in those with multiple metastatic lesions. Thirty-one chemotherapy-naive patients with metastatic breast cancer (36% with single metastatic site) were treated with vinorelbine (30 mg/m^2 on day one), mitoxantrone (10 mg/m^2 on day one), and carboplatin (250 mg/m^2 on day two), every three weeks. Overall response rate in 29 evaluable patients was 65%, with two CRs (7%) and 17 PRs (58%). In addition, disease stabilized in four patients (14%) and progressed in six (21%). Chemotherapy, administered on an outpatient basis, was generally well tolerated. Prophylactic use of hemopoetic growth factors prevented severe myelotoxicity. Best responses were seen in lung and soft tissues, but important responses also were also observed in other sites, including the liver. Median time to disease progression was 7.1 months (range 1-16 months). Median duration of survival was 11 plus months (range 2-21 months) (Kakolyris S etal, Abstracts of the 6th ICAT, Pg 159:#123).

Patients with advanced breast cancer treated with weekly epirubicin plus vinorelbine benefited from high dose regimens by the addition of G-CSF. Thirty-two chemotherapy-naive women were treated with a combination regimen of epirubicin (25 mg/m^2) and vinorelbine (25 mg/m^2), administered weekly, along with G-CSF (300 mg/day, subcutaneously, three times a week). At the time of the report, among 27 evaluable patients, the objective response rate was 74%, with four CRs (14.8%) and 16 PRs (59.2%). Another seven patients experienced stable disease. In six months of treatment, no disease progression was seen. Furthermore, in a 20 month follow-up, median duration of response in patients with CR was 18 months and, in persons with PR, 10.7 months. This regimen requires that G-CSF is administered in the first six weeks

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

of treatment because of higher than grade II neutropenia, without any serious infection. Use of G-CSF permitted a high dose-intensity equal to 86% of the theoretically desired dose. Furthermore, activity of this drug combination occurred irrespective of the prognosis of the various patient subgroups (Terzoli E, etal, Abstracts of the 6th ICAT, Pg 71:#121).

Combination of vinorelbine and ifosfamide was also shown to be active in patients with metastatic breast cancer who failed anthracycline-based chemotherapy. In a phase II clinical trial, 25 women with metastatic breast cancer resistant to first-line anthracycline therapy, were treated with ifosfamide (1000 mg/m^2 daily, as a two-hour IV infusion on days one to five) plus vinorelbine (25 mg/m^2 on day one and eight), every three weeks. Mensa was administered IV at 20% of the ifosfamide dose at time 0 and, orally, at 40% of the ifosfamide dose, at hours four and eight. Drug-related toxicity was acceptable and no life threatening side effects were seen. Chief adverse effects were nausea and vomiting, leukopenia, anemia, alopecia, and mucositis, but all were at grade 1-2 level. The overall objective response rate was 28%, with seven PRs. Disease stabilized in ten women (40%) and progressed in 30%. Median duration of response was four months, with a range of 2-12+ months (Queirolo P, etal, Abstracts of the 6th ICAT, Pg 70:#118).

Gemcitabine (Gemzar; Eli Lilly) in combination with doxorubicin exhibited promising activity, with modest toxicity, in patients with advanced breast cancer. Twenty-one chemotherapy-naive women with metastatic breast cancer were treated with gemcitabine as a 30-minute infusion on days one, eight, and 15 of each 28 day cycle, with the first six receiving a dose of 800 mg/m^2 weekly, the second six 1000 mg/m^2 weekly, and the last nine 800 mg/m^2 weekly; doxorubicin (25 mg/m^2) was administered after gemcitabine. In 19 evaluable patients, the overall objective response rate was 68.4%, with 3 CRs and 10 PRs; disease stabilized in three. Hematologic adverse events were grade 3-4 neutropenia (14 patients) and grade 3-4 thrombocytopenia (4 patients). Two of six patients on doxorubicin and gemcitabine (1000 mg/m^2/weekly) died, one from bleeding complications with severe myelosuppression (possibly drug-related), and the other from bilateral pneumonia and septic shock with mild neutropenia (not thought to be drug related). Gemcitabine (800 mg/m^2 weekly) is recommended in combination with doxorubicin because of the more favorable toxicity profile (Perez-Manga G, etal, Abstracts of the 6th ICAT, Pg 69:#11-5).

FILM, a combination regimen of 5-FU, ifosfamide, leucovorin, and mitomycin, resulted in response rates beyond expectation, with only moderate toxicity, in women with metastatic, locally advanced, or inoperable breast cancer. Twenty-four chemotherapy-naive patients were treated with up to six 21-day cycles of FILM on an outpatient basis. Each cycle consisted of 5-FU (750 mg/m^2), ifosfamide (1 g/m^2 and mensa at a 100% of ifos-famide dose), and leucovorin (200 mg/m^2) given on day one. Mitomycin C (6 mg/m^2) was given at alternate cycles. Dose reduction and dose delay were permitted. Twenty-two women completed six courses of FILM. The total objective response rate was 83%, with 9 CRs and 10 PRs. Following completion of chemotherapy, the women were treated by mastectomy, radiotherapy, or tamoxifen. One year after completion, 18 patients (75%) remain alive and in remission. With regard to toxicity, 11 cycles were delayed because of slow recovery of the white blood cells, but no dose reductions were required. Two blood transfusions were needed for anemia. The most frequent drug-related toxicities were nausea (17 patients), fatigue (15 patients), and vomiting (9 patients), but none reached grade 4 severity (Davidson N, etal, Abstracts of the 6th ICAT, Pg 64:#93).

INTRA-ARTERIAL CHEMOTHERAPY

Intra-arterial chemotherapy (IAC) is an effective, well-tolerated treatment for women with recurrent breast cancer, resistant to other treatment modalities. Thirty-nine patients with recurrent breast cancer were treated with superselective IAC, using mitoxantrone (25 mg/m^2), over a period of 24 hours. The drug was infused via sidebranches of the subclavian artery under heparin administration. The extent of tumor perfusion was controlled with angio-CT imaging. IAC was repeated every three to six weeks from one to nine times. Prior to IAC, all patients had undergone radiotherapy, 51% had undergone repeated surgical procedures, and 59% were exposed to systemic chemotherapy. Overall response rate was 75% (21% CRs and 54% PRs), and 8% experienced disease progression. Remission following IAC was also observed in patients with mediastinal or lymph node involvement. Seven women are still under treatment. However, 23% of patients died from systemic tumor spread and 36% developed distant metastases within 18 months while undergoing therapy. Side effects were moderate and did not affect patients' quality of life (Gorlich J, etal, Abstracts of the 6th ICAT, Pg 232:#714).

INDEX OF COMPANIES & INSTITUTIONS

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.

INDEX OF COMPANIES & INSTITUTIONS

FUTURE ONCOLOGY

PUBLISHED BY **NEW MEDICINE, INC.**

PUBLISHER AND EDITOR: **Katie Siafaca, MS**

EPIDEMIOLOGY: **Anita Valabhji, MPH**

RESEARCH ASSOCIATES: **Sarah Nghiem, Brandon Wong and Fred Hall**

DESIGN & PRODUCTION: **Jill Burch**

EDITORIAL BOARD

BIOTECHNOLOGY & APPLIED SCIENCES:
James W. Hawkins, PhD, Editor, Antisense Research and Development

CLINICAL PRACTICE:
Ante Lundberg, MD, Dana-Farber Cancer Institute and Harvard Medical School

REIMBURSEMENT AND MANAGED CARE:
Elan Rubinstein, PharmD, MPH, Consultant

TECHNOLOGY AND DEVICES:
Marvin Burns, MBA, President, Bio-Tech Systems

NEW MEDICINE, INC. MAILING ADDRESS:

P.O. Box 909
Lake Forest, California 92630
Tel: 714. 830. 0448 ■ Fax: 714. 830. 0887
e-mail: newmedinc@aol.com
www:http://www.wp.com/new_med/

SUBSCRIPTION INFORMATION:

- FUTURE ONCOLOGY (ISSN 1082-331X) is published as 10 issues (two double issues) per year, with a free annual index listing companies/institutions and subjects covered.
- A one-year subscription, (issues V1 #7 to V2 #6), sent first class to U.S. addresses is US $720. A one-year subscription, sent air mail to addresses outside the U.S., is US $780.
- One-year's subscription plus back issues (V1, #1-#6) is $1,000 (U.S.) and $1,100 (outside the U.S.).
- Additional subscriptions sent in the same envelope are $390 each.
- Back issues (V1, #1-#6) are $350.
- Payment must accompany your order; checks must be drawn on a U.S. bank. (A purchase order number is acceptable; however, the subscription will not begin until payment is received.) Make checks payable to New Medicine. Payment may also be made by AMERICAN EXPRESS, VISA or MASTERCARD and wire transfer; please call 714. 830. 0448.

SALE OF FUTURE ONCOLOGY IS MADE UNDER THE FOLLOWING CONDITIONS:

1) Unauthorized photocopying, distribution or electronic storage is strictly prohibited. 2) Information published in Future Oncology is developed from various sources believed to be reliable. There can be no assurance that such information is accurate in all respects, however, and the publisher cannot be held liable for errors. Errors, when discovered, will be corrected. 3) Subscriptions may not be canceled, but may be transferred.

COPYRIGHT © 1996 NEW MEDICINE, INC. 714. 830. 0448.