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

### LYMPHOMA/MULTIPLE MYELOMA

Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) are malignancies whose cell of origin is the human lymphocyte. With the exception of NHL, these malignancies are generally rare and their incidence varies by geographic area and within racial and ethnic groups. For instance, HD is less common in Asia, while multiple myeloma is more common in blacks. Also, other contributing factors may play a role in such incidence variations; for instance, higher incidence rates of NHL in the USA may be attributed to the emergence of HIV-associated NHL. Estimated incidence of lymphoma and multiple myeloma in the USA, Europe and Japan is presented in Exhibits 1 and 2. Mortality data was presented in FO, V1, #9.

#### EPIDEMIOLOGY, ETIOLOGY AND CLASSIFICATION

##### Hodgkin's Disease (HD)

Named for the pathologist who originally described the disease, Hodgkin's disease (HD) is derived from activated lymphoid cells. HD is rare in the USA, estimated to occur in 3 of every 100,000 persons. In 1995 approximately 7,800 cases of HD were diagnosed in the USA (see Exhibit 1). Incidence is higher in whites than blacks and in men than women. Although median age at diagnosis of HD is 32, there is a bimodal distribution pattern of incidence in developed countries, with peak risks occurring in the age groups 20-24 years and 80-84 years. In underdeveloped countries, the overall incidence is lower with the exception of the under 15 years-of-age group. Both incidence and mortality associated with HD have been declining in the USA at an estimated annual rate of 1% and 2.8%, respectively.

The etiology of HD is attributed to multiple causes, including hereditary, viral, environmental, occupational and socio-economic factors. For instance, there is an association with woodworkers and after tonsillectomy and appendectomy, as well as a familial association. Also, there seems to be an association between HD and infection with Epstein-Barr virus (EBV) because the latter is detectable in almost 50% of Reed-Sternberg cells in HD biopsies. A link between HIV infection and HD, suggested by various epidemiologic studies, remains unproven.

Hereditary factors may also be implicated because HD occurs preferentially in certain families and relatives of young adults with HD are at an increased risk (three- to seven-fold higher among siblings). In a study of 187 pairs of dizygotic and 179 pairs of monozygotic twins from families affected with HD, 10 pairs of identical twins were affected compared to an anticipated 0.1 cases that occur by chance. All cases occurred before age 50 (Mack TM, NEJM, Feb 16, 1995, 332:413-418). The basis of any genetic susceptibility to HD remains obscure but an

association has been suggested with an HLA-linked recessive susceptibility gene which may be implicated in 60% of familial HD.

Hodgkin's disease is unlike other malignancies in that most of the palpable tumor consists of normal inflammatory cells. The malignant cells are the distinctive Reed-Sternberg cells which make up a minority of the tumor. Although diagnosis of HD can rarely be made without the presence of Reed-Sternberg cells, these cells are also seen in infectious mononucleosis and other malignancies.

Classification of HD is based on pathologic examination, with subtypes named according to histologic appearance as nodular sclerosing (NS), lymphocyte predominant (LP), lymphocyte depleted and mixed of cellularity. Nodular sclerosing HD is the most common type at diagnosis, affecting 80% of patients, and is the least advanced. The other subtypes tend to be associated with more advanced disease at presentation. For instance, HD of mixed cellularity is most often (40%-50% of cases) the primary type found in newly-diagnosed HIV+ patients with HD and is more common among elderly HD patients.

Substantial gains in survival were achieved in the past 20 years in HD, mostly attributed to the use of combination chemotherapy, first applied successfully in the early 1970s. Survival outlook is determined by stage of disease at diagnosis and histologic subtype. Overall, five-year survival rate is estimated at 80%, ranging from 86.8% for those under 45 years-of-age to 31.9% for those over 75 years-of-age (see Exhibit 1).

##### Non-Hodgkin's Lymphoma (NHL)

Non-Hodgkin's lymphoma (NHL) arises from the clonal expansion of a compartment of the human lymphoid system. NHL has become the fourth most common type of cancer in the USA, with an incidence of approximately 19.3 (15.1 age-adjusted) per 100,000 population. Incidence of NHL has been increasing over the past fifty years at 2% to 3% per year; it increased over 65% between 1973 and 1990, representing one of the largest increases for any cancer. This rise was particularly steep (90%) in men under age 65, compared to 40% in women in the same age group. NHL incidence also rises with increasing age, with rates ranging from 1/100,000 in the 5-9 years-of-age group to 82.5/100,000 in those over 85 years-of-age. Mortality has also increased significantly (about 2.8% per year) in the 1987-1991 period. Annual incidence of NHL is currently estimated at 50,900 in the USA, resulting in 22,700 deaths. In contrast, incidence of Hodgkin's disease has been stable and survival improved significantly. Rising incidence combined with lower survival rates (about 50% at five years), has resulted in NHL being the cause of over 90% of lymphoma deaths as compared to 60% in 1950.

Reasons for the rise in NHL incidence rates is unclear but may be partially attributed to a rise in AIDS-associated NHL since the beginning of the HIV pandemic.

**Exhibit 1**  
**Estimated Incidence and Five-Year Survival Rates Associated with Lymphoma/Multiple Myeloma**

INCIDENCE						
Type of Malignancy	Male (#)	Rate*	Female (#)	Rate*	Total (#)	Rate*
Hodgkin's Disease	4,500	3.5	3,300	2.4	7,800	3.0
Non-Hodgkin's Lymphoma	29,500	22.9	21,400	15.9	50,900	19.3
Multiple Myeloma	7,100	5.5	5,400	4.0	12,500	4.8
<b>TOTAL</b>	<b>41,100</b>	<b>31.9</b>	<b>30,100</b>	<b>22.3</b>	<b>71,200</b>	<b>27.1</b>

  

FIVE-YEAR SURVIVAL						
Type of Malignancy	Male (#)	Total (%)	Female (#)	Total (%)	Total (#)	Total (%)
Hodgkin's Disease	3,447	76.6	2,703	81.9	6,150	78.8
Non-Hodgkin's Lymphoma	14,721	49.9	11,684	54.6	26,468	52.0
Multiple Myeloma	2,024	28.5	1,453	26.9	3,463	27.7
<b>TOTAL</b>	<b>20,192</b>	<b>49.1</b>	<b>15,840</b>	<b>52.6</b>	<b>36,081</b>	<b>50.7</b>

Source: Adapted from SEER Cancer Statistics Review, 1973-1991, and Cancer Statistics 1995 from the American Cancer Society  
\* per 100,000 population

A more rapid increase in incidence, seen among men under 65 years-of-age, is attributed to more diagnoses of NHL "secondary to HIV infection". The impact of HIV on the incidence of NHL in recent years is best illustrated by particularly dramatic increases in NHL occurrences among men, aged 20-54 years, in the San Francisco/Oakland area. These increases lag, by a couple of years, the increases seen in Kaposi's sarcoma. Excluding incidence rates from HIV+ men from overall increases in NHL incidence among 20-54 year-old men, results in much lower age-adjusted rates (14.2 versus 11.7 per 100,000 in 1993, respectively). However, even with this exclusion, an increase remains in NHL incidence in this group as well as those 55 years-of-age and over.

Occupational exposure seems to play a role because those working in farming, paper processing and other professions which involve exposure to herbicides and solvents, have a higher risk of developing NHL. Indeed, a dose-response has been demonstrated between the number of acres sprayed with herbicides and the risk of developing NHL. In addition to HIV/AIDS, other risk factors include genetic immunodeficiencies (Wiskott-Aldrich syndrome, ataxia telangiectasia, and common variable immunodeficiency), immunodeficiency associated with organ transplantation and chemotherapy and autoimmune disorders such as rheumatoid arthritis, Hashimoto's thyroiditis or celiac sprue. These conditions are most likely associated with hyperactivity of a damaged immune system leading to loss of growth control.

It is also clear that several viruses are associated with the development of NHL. Epstein-Barr virus (EBV) is

associated with 98% of cases of epidemic Burkitt's lymphoma, but only 15-20% of nonendemic cases. EBV is associated with 50% of AIDS-associated NHL. It is postulated that lymphomagenesis requires immunodeficiency and a polyclonal expansion of cells secondary to EBV. After a second event, a malignant clone emerges and gives rise to lymphoma. About 1% of individuals infected with human T cell lymphoma virus type 1 (HTLV-1) develop an aggressive form of T cell lymphoma. The mechanism by which infection with this retro-virus leads to malignant transformation is unknown. T cell

lymphoma associated with HTLV-1 is generally rare but occurs with higher frequencies in certain geographic areas (see FOV1, #9).

NHL may be classified using several systems (see Exhibit 3). Much of the original terminology was established by the Rappaport system, introduced nearly 50 years ago. This has now been supplanted by the more popular Working Formulation, introduced in the early 1980s. The main attraction of this system is that it divides NHL into three broad categories, low-, intermediate- and high-grade, which associate types of lymphoma with similar presentations, natural histories and response to therapy. NHL may also be classified by the cell involved as T cell or B cell; the majority of NHL is of the B cell type.

Low-grade NHL probably accounts for 40% to 50% of cases and the median survival, based on natural history of the disease, is measured in years. Intermediate-grade NHL accounts for about 45% of cases and its natural history is measured in months. High-grade NHL represents about 5-12% of cases and survival for untreated patients is measured in weeks. Burkitt's lymphoma is a high-grade NHL that is endemic in tropical Africa, South America and southeast Asia, as well as sporadic in other parts of the world.

Several additions and modifications may be incorporated to make this classification system more useful. A new proposed classification system, the revised European-American classification of lymphoid neoplasms (REAL), has attempted to incorporate modern advances in immunology, cytogenetics and molecular genetics to

**Exhibit 2**  
**Estimated Incidence of Lymphomas and Multiple Myeloma in the USA, Canada, Europe\* and Japan in 1995**

Malignancy	Total (#)	Total (%)	Europe (#)	Total (%)	USA and Canada (#)	Total (%)	Japan (#)	Total (%)
Hodgkin's Disease	28,062	16.2	17,648	62.9	8,560	30.5	1,854	6.6
Non-Hodgkin's Lymphoma	113,177	65.4	45,054	39.8	57,000	50.4	11,123	9.8
Multiple Myeloma	31,849	18.4	14,881	46.7	13,260	41.6	3,708	11.7
<b>TOTAL</b>	<b>173,088</b>	<b>100.0</b>	<b>77,583</b>	<b>44.8</b>	<b>78,820</b>	<b>45.5</b>	<b>16,685</b>	<b>9.7</b>

\* Excludes the former USSR

enhance staging. According to REAL, immunoblastic NHL should be grouped with diffuse large cell lymphoma because of a similar natural history and response to treatment. Mantle cell lymphoma, a relatively new pathologic entity, is unique in that it shares the speed of growth of intermediate-grade NHLs, yet has the recalcitrant nature of low-grade lymphomas. Two other newer pathologic entities are mucosa-associated lymphoid tumors (MALT) and monocytoid B cell lymphomas which are best classified with small lymphocytic lymphoma. Anaplastic large cell lymphoma, usually positive for the antigen Ki-1, which has been confused in the past with Hodgkin's disease, is most similar to diffuse large cell lymphoma. T cell rich B cell lymphoma, another new entity, is a B cell malignancy similar to large cell NHL but can be confused for a T cell disease because of the large number of infiltrating T cells. Only about 15% of large cell NHLs have a T cell phenotype. Lymphoblastic lymphoma and anaplastic large cell lymphoma are usually of T cell type; most other subtypes of NHL are nearly always of B cell origin.

Five-year survival rates for NHL (see Exhibit 1) have remained relatively unchanged since 1974, rising from 47.1% to 52% in 1990. Because of its association with HIV/AIDS these rates are not expected to improve in the near future.

### Multiple Myeloma

Multiple myeloma is a malignancy involving the plasma cell, usually characterized by the presence of a monoclonal immunoglobulin in serum and/or urine. The term, multiple myeloma was coined to reflect the multiple sites of bone involvement. Multiple myeloma mostly occurs in later life, particularly in older black men and women. Incidence is 5.1/100,000 in white men, 3.1/100,000 in white women, 12.0/100,000 in black men and 8.0/100,000 in black women. Incidence of multiple myeloma increases with age. Only 1% of cases occur in patients under 40 years old, and 19.4% in those under 60 years of age. Multiple myeloma incidence rates declined at about 1% per year in the 1987-1991 period but death rates increased by 1.7%. Approximately 12,500 cases of multiple myeloma were diagnosed in the USA in 1995.

Although the cause of multiple myeloma remains unknown, potential risk factors include exposure to radiation or petroleum products. A less than two-fold risk was found in farmers, paper producers, furniture makers and woodworkers. The theory that repeated chronic antigenic stimulation of the immune system is a risk factor in the development of this disease was not supported in a recent study of 573 cases of multiple myeloma (Lewis DR, et al, Cancer Causes and Control, 1994 Nov, 5(6):529-39).

Hereditary factors may also play a role because multiple myeloma occurs among family members. The discovery of specific human leukocyte antigens (HLA) and chromosome abnormalities such as translocation t(11;14)(q13;q32) which may be involved in the genesis of multiple myeloma by altering the structure or function of oncogenes or tumor suppressor genes, indicates a genetic predisposition for this cancer. There seems to be almost a universal presence of activated oncogenes and tumor suppressor genes in the plasma cells of patients with multiple myeloma which are associated with the accumulation of a variety of secondary genetic changes accelerating malignant transformation.

Both major and minor criteria for the diagnosis of multiple myeloma have been established based on laboratory findings, radiographic studies and bone marrow analysis (see Exhibit 4). Diagnosis can be made with any two major criteria or a combination of major criterion 1 plus minor criterion b, c, or d; major criterion 3 plus minor criterion a or c; or minor criteria a, b and either c or d.

The prognosis for multiple myeloma is generally poor with overall five-year survival rates estimated at 27.7% (see Exhibit 1). Survival is poorest in those over 65 years-of-age (22.1%) compared to those under 65 (36.0%). Since 1973, there has been little improvement in survival rates.

### PRESENTATION, DIAGNOSIS AND STAGING

#### Hodgkin's Disease

HD patients usually present with painless lymphadenopathy. Diagnosis can only be made with lymph node biopsy, with documentation of the presence of

Reed-Sternberg cells. Immunophenotyping reveals that the majority of tumor cells express antigens CD15, CD30 and LN2. Presence of these markers can help distinguish HD from NHL. Staging has been used to differentiate those patients who require systemic chemotherapy from those that may be treated with radiation therapy. The staging is according to the Ann Arbor system. Stage I disease is limited to a single lymph node region, stage II involves two lymph node groups on the same side of the diaphragm, stage III involves both sides of the diaphragm and stage IV involves an extranodal site. The patients are further classified as to whether B symptoms are present (B) or not (A). B symptoms include fever above 38 degrees C, night sweats or weight loss of at least 10% of body weight. The presence of B symptoms usually indicates more extensive disease.

Staging is accomplished with history, physical examination, laboratory studies and radiographic procedures such as CT scans of the chest and abdomen, and gallium scanning. If the patient appears to have stage I or II disease, then radiotherapy alone can be highly curative. Despite negative staging, 10-35% of patients will still have disease found if an exploratory laparotomy is performed. This "staging laparotomy" includes splenectomy, liver biopsy from both lobes, and biopsy of bilateral paraortic, splenic hilar, hepatic, mesenteric and iliac nodes. After all staging procedures, approximately 40% of patients will have stage I or II disease. The risk of finding disease at laparotomy is low enough to obviate surgery in some patients, especially young women with stage I disease and NS or LP histology.

### Non-Hodgkin's Lymphoma

The majority of patients with NHL present with palpable lymphadenopathy. Other symptoms include blood cytopenias secondary to bone marrow infiltration or immune destruction, abdominal mass, obstruction of a tubular organ secondary to lymphadenopathy, or constitutional, or B symptoms. Diagnosis cannot be

established without biopsy of involved tissue, preferably a lymph node rather than extranodal tissue. Evaluation of extent of disease includes physical examination, CT scan of the abdomen and pelvis, chest x-ray, bone marrow biopsy and, in appropriate cases, gallium scanning.

In addition to histologic differences, each lymphoma subtype has been associated with some chromosomal abnormality. The most common abnormalities are translocations involving the antigen receptor genes; the T cell receptor in T cell lymphomas and immunoglobulin genes in B cell lymphomas. There are specific cytogenetic defects which correlate with certain histologies of NHL. The c-myc translocation, found in all cases of Burkitt's lymphoma, involves translocations t(8;14), t(2;8) or t(8;22) of the c-myc oncogene from chromosome 8 to the immunoglobulin genes on chromosomes 14, 2 or 22, which lead to overexpression of this oncogene.

The t(14;18) translocation is present in 85%-90% of follicular NHL (low-grade). Translocation of the bcl-2

<b>Exhibit 3</b>			
<b>Estimated Incidence of NHL by Grade and Type in the USA in 1995</b>			
<b>Working Formulation</b>	<b>Rappaport Classification</b>	<b>Incidence (#)</b>	<b>Rate*</b>
<b>LOW-GRADE MALIGNANT LYMPHOMA (22.2%)</b>		<b>11,311</b>	<b>5.6</b>
A. Small lymphocytic lymphoma (SLL); B cell, rarely T cell	Diffuse well-differentiated lymphocytic (DWDL)	4,325	1.6
B. Follicular, predominantly small cleaved cell (FSCL); B cell	Nodular poorly differentiated lymphocytic (NPDL)	4,325	1.6
C. Follicular mixed, small cleaved and large cell (FML); B cell	Nodular mixed histiocytic-lymphocytic (NML)	2,661	1.0
<b>INTERMEDIATE-GRADE MALIGNANT LYMPHOMA (42.5%)</b>		<b>21,624</b>	<b>8.2</b>
D. Follicular predominantly large cell (FLCL); B cell	Nodular histiocytic (NHL)	1,331	0.5
E. Diffuse small cleaved cell (DSCL); B cell and sometimes T cell	Diffuse poorly differentiated lymphocytic (DPDL)	2,661	1.0
F. Diffuse mixed, small cleaved and large cell (DML); either B cell or T cell	Diffuse mixed histiocytic-lymphocytic (DML)	2,661	1.0
G. Diffuse, large cell (DLCL); either B cell or T cell	Diffuse histiocytic (DHL)	14,971	5.7
<b>HIGH-GRADE MALIGNANT LYMPHOMA (12.4%)</b>		<b>6,321</b>	<b>2.4</b>
H. Large cell, immunoblastic (IBL); either B cell or T cell	Diffuse histiocytic (DHL)	3,992	1.5
I. Lymphoblastic (LBL); thymic T cell	Diffuse lymphoblastic	333	0.1
J. Small non-cleaved cell and Burkitt's lymphoma (SNCL); B cell	Diffuse undifferentiated pleomorphic (DUL)	1,996	0.8
<b>UNCLASSIFIED GRADE MALIGNANT LYMPHOMA (22.8%)</b>		<b>11,644</b>	<b>4.4</b>

Source: Adapted from SEER Cancer Statistics Review, 1973-1991 and Cancer Statistics 1995 from the American Cancer Society

\* per 100,000 population

**Exhibit 4**  
**Criteria for Diagnosis of Multiple Myeloma**

Major Criteria	Minor Criteria:
1. Plasmacytomas on tissue biopsy	a. Bone marrow plasmacytosis(10-30% plasma cells)
2. Bone marrow plasmacytosis (>30% plasma cells)	b. Monoclonal immunoglobulin spike present but less than in criterion 3
3. Monoclonal immunoglobulin spike on serum electrophoresis - IgG > 3.5 g/dl or IgA > 2.0 g/dl; kappa or lambda light chain excretion > 1.0 g/day on 24-hour urine protein electrophoresis	c. Lytic bone lesions
	d. Normal IgM <50 mg/dl, IgA <100 mg/dl, or IgG <600 mg/dl

gene, located on chromosome 18, leads to its upregulation and thus disruption of normal senescence of the follicular center cell, preventing apoptosis. Translocation t(11;14), commonly found in mantle cell lymphoma, leads to deregulation of *bcl-1*, which is involved in the regulation of cell division. Large cell NHL has been associated with translocations involving *c-myc*, *bcl-2* and *bcl-6*. The latter is located on chromosome 3 and is required to regulate cell proliferation and differentiation. High expression of *bcl-2* in large cell lymphoma cells is associated with poor prognosis.

Staging of NHL also uses the Ann Arbor system which divides patients into limited disease (stage I or II, bulk less than 10 cm and no B symptoms) and extensive disease (stage III or IV, bulk greater than 10 cm or B symptoms). In addition, an International Prognostic Index for intermediate-grade NHL (plus immunoblastic) has been devised (Shipp, Blood 1994;83:1165-1173). In this index, one point is assigned for each independent risk factor. These factors are age greater than 60; stage III or IV; performance status greater than 1; lactate dehydrogenase level (LDH) greater than normal; and number of extranodal sites greater than 1. The number of factors present is highly predictive of long term survival; 73% of those with one factor survive 5 years, compared to 51% with two factors, 43% with three and 26% with four or five factors.

### Multiple Myeloma

The most common presenting symptoms arise from lytic bone lesions, depressed bone marrow function and deposition of myeloma proteins in the kidney. These symptoms include bone pain, anemia, renal insufficiency and hypercalcemia and their sequelae. At the time of diagnosis most multiple myeloma patients have osteolytic lesions and 30% also have hypercalcemia. These complications are major causes of morbidity causing cachexia, bone pain, fractures, spinal cord compression and renal insufficiency. These findings are in addition to the diagnostic criteria of monoclonal immunoglobulins, radiographic abnormalities and bone marrow abnormalities.

Quantitation of the number of monoclonal plasma cells in the peripheral blood of newly-diagnosed untreated

multiple myeloma patients may be an independent prognostic factor for survival (Witzig TE, et al, Blood, Vol 86, No 10, Supplement to Nov 15, 1995, Abs. 217).

The most commonly used staging system is the Durie-Salmon system (see Exhibit 5). Despite the development of several staging systems designed to predict prognosis, one of the most powerful predictors of prognosis is serum  $\beta$ -2 microglobulin levels. This protein represents the light chain of the major histocompatibility complex of the cell membrane. Increased levels are the result of release of this protein by tumors with a high growth fraction. These levels tend to correlate with stage of disease as defined by the Durie-Salmon system.

### TREATMENT OPTIONS: RADIATION THERAPY, CHEMOTHERAPY AND BONE MARROW TRANSPLANTATION

Chemotherapy, radiation therapy and bone marrow transplantation are all used to treat lymphomas/multiple myeloma. This group of diseases is only second to leukemias as an indication for bone marrow transplantation (BMT). However, in contrast to leukemias where allogeneic BMT (alloBMT) is the primary approach, autologous BMT (autoBMT) and/or peripheral blood stem cell (PBSC) transplants is the approach of choice in lymphoma and multiple myeloma (see Exhibits 6, 7 and 8), representing 88.8% of all transplants in the USA and 92.6% in Europe.

Treatment for advanced stages of these malignancies is often associated with increased morbidity requiring multiple hospitalizations. In the USA, according to the National Center for Health Statistics (see Exhibit 9), there were approximately 80,000 cases (first-listed diagnosis) of hospitalizations for the treatment of NHL and multiple myeloma in 1993; overall, approximately 200,000 hospitalizations involved cases where these malignancies, as well as HD, were present (all-listed diagnosis).

### Hodgkin's Disease

Mantle irradiation, involving radiation therapy to the lymph nodes of the neck, axilla and mediastinum, is the treatment of choice for stage I and II supradiaphragmatic

HD. This approach results in a cure rate of approximately 80% (Mauch, et al, JCO 1988; 6:1576-1583). For patients who relapse after initial radiation therapy, salvage chemotherapy is also effective, with a cure rate of about 70% (Mauch, et al, Blood 1980; 56:892-897). Risk factors for relapse include involvement of 4 or more nodal groups, mediastinal mass greater than 1/3 diameter of the chest, splenic involvement greater than 4 nodules and B symptoms.

For patients with more advanced disease, combination chemotherapy has resulted in cure rates of approximately 60% (Longo, et al, JCO 1986;4:1295-1306). The longest experience, over 20 years, has been with the MOPP (nitrogen mustard, vincristine, procarbazine and prednisone) regimen. Newer regimens, particularly ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), appear to be as efficacious with lower toxicity. For patients who relapse after initial chemotherapy, second-line chemotherapy offers a chance for cure related to the duration of the first remission. For those who relapse within less than 12 months from remission or who experienced incomplete remission, treatment with alternative therapy results in a cure in only 20-25% of cases (Canellos, et al, NEJM 1992;327:1478-1484). This outcome is improved to 50% for patients who experienced complete remission (CR) of at least 12 months duration. Prognostic factors for duration of CR include disease stage, number of extranodal sites, elevated alkaline phosphatase or erythrocyte sedimentation rate, age, B symptoms, bone marrow involvement and rate of response to chemotherapy.

Bone marrow transplantation has also been gaining ground in the treatment of relapsed HD.

### Non-Hodgkin's Lymphoma

Cure rates for NHL have been disappointing, with almost 50% of patients dying within 5 years. Although various established chemotherapy regimens produce remissions, usually patients relapse and second and third rounds of treatment using conventional chemotherapy produce diminishing returns. The newest chemotherapy agents with activity in NHL, particularly in low-grade disease, are the purine analogs, fludarabine, deoxycoformycin and chlorodeoxyadenosine (see FO, V1, #9 pp 213-214). These agents have resulted in response rates of 25-50% in relapsed patients but, similarly to other chemotherapy agents, they usually fail to effect a long-lasting cure.

For patients who relapse after initial chemotherapy, there exists a possibility of cure with high-dose chemotherapy and autologous BMT. The complete response rate is about 50% and cure rates vary from study to study, but are in the range of 40%. There are several factors that can help predict which patients will

**Exhibit 5  
Durie-Salmon System for Multiple Myeloma Staging and Survival by Stage and Type**

STAGE	STAGING CRITERIA
Stage I	Hemoglobin greater than 10 grams (g)/liter(l) Calcium less than 12 milligram (mg) per deciliter (dl) Normal bone x-rays Low levels of monoclonal immunoglobulins
Stage II	Values between stage I and III
Stage III	Hemoglobin (hgb) less than 8.5 g/l Calcium greater than 12 mg/dl Advanced bone lesions High monoclonal immunoglobulin levels
A patients	Serum creatinine less than 2 mg/dl
B patients	Serum creatinine higher than 2 mg/dl
MEDIAN SURVIVAL (MONTHS)	
Stage IA	61
Stage IB, IIA or IIB	54.5
Stage IIIA	30
Stage IIIB	15
Serum $\beta$ -2 microglobulin level of less than 7.6 mg/dl	44
Serum $\beta$ -2 microglobulin level greater than 7.6 mg/dl	12

benefit from this treatment approach, including a good performance status, duration of remission, chemotherapy-sensitive disease and minimal tumor burden. Because initial and second-line therapies are usually so successful, patients who fail to respond are generally poor candidates for trials of novel treatments as there is often advanced disease, poor bone marrow reserve and poor performance status.

Treatment approaches in NHL are determined by a number of factors, including histologic subtype (and therefore anticipated natural history), stage (extent of disease) and physiologic status of the patient (ability to tolerate therapy). The Working Formulation divides the NHLs into three distinct grades based on their natural history and response to treatment. Because the grade is the most important predictor of survival, and treatment approaches vary, each grade is discussed separately.

**Exhibit 6  
Hospitalization of Lymphoma/Multiple Myeloma Patients in the USA (1993)**

ICD-9-CM	FIRST-LISTED DIAGNOSIS			ALL-LISTED DIAGNOSIS		
	Total (#)	Male (%)	Aged over 65 years (%)	Total (#)	Male (%)	Aged over 65 years (%)
200. Lymphosarcoma & reticulosarcoma	12,000	67.0		29,000	62.1	55.2
200.0 Reticulosarcoma				17,000		58.8
202. NHL	40,000	45.0	47.5	92,000	47.8	52.2
201. Hodgkin's Disease				22,000		35.0
203. Multiple Myeloma	28,000	64.3	57.1	67,000	55.2	68.7

Source: National Center for Health Statistics (1993)

**Exhibit 7  
Estimated Allogeneic and Autologous Transplants for Lymphoma/Multiple Myeloma in the USA (1993)**

Indication	Total (#)	Total (%)	Allogeneic (#)	Total (%)	Autologous (#)	Total (%)
NHL	1,824	63.8	198	10.8	1,626	89.2
HD	682	23.9	30	4.4	652	95.6
Multiple Myeloma	353	12.3	93	26.2	260	73.7
<b>TOTAL</b>	<b>2,859</b>	<b>100.0</b>	<b>321</b>	<b>11.2</b>	<b>2,538</b>	<b>88.8</b>

*Low-grade NHL* treatment is the most controversial subject in the management of lymphoma. Lymph node morphology of small lymphocytic lymphoma and chronic lymphocytic lymphoma are indistinguishable and both entities are considered disseminated at diagnosis. Follicular lymphomas are so named because they exhibit follicular, or nodular, features from their site of origin, the follicular center cell of the lymph node. Follicular lymphoma consists of three subtypes, small cell, mixed small and large cell, and large cell, based on the number of large cells present. It is important to identify the 10-15% of patients who present with early stage (I or II) disease because they may be cured with local radiotherapy. The experience of the Princess Margaret Hospital (Toronto, Canada) and the National Cancer Institute of Canada confirm a cure rate of approximately 50% for patients with stage I and II follicular lymphoma treated with radiation therapy alone.

For patients with advanced stage disease, extensive clinical investigation has failed to prove that immediate aggressive therapy improves survival compared to observation with therapy as required for palliation. This is despite the fact that low-grade lymphomas are highly responsive to chemotherapy and radiation. Unfortunately, remissions last a median of only 2 years and fewer than 10% last 5 years. This disease remains resistant to cure with standard therapy. However, even without durable responses, median survival for this group of

patients is 9 years because of the long natural history of the disease.

Despite the lack of curative efficacy of chemotherapy in patients with follicular lymphoma, there is evidence that patients with follicular mixed NHL may benefit from combination chemotherapy, as nearly half of those treated will be without signs of disease at 10 years. In addition, follicular large cell lymphoma is considered curative and is included in the intermediate-grade category. A possible explanation for this variable response among follicular lymphoma is that as the percentage of large cells in follicular lymphoma increases, the growth fraction of the tumor increases and the tumor becomes more susceptible to eradication by chemotherapy.

In distinction, follicular small cleaved cell lymphoma and small lymphocytic lymphoma are comprised of cells that are not in cell cycle and, therefore, not sensitive to chemotherapy. This is analogous to the pluripotent stem cell and its resistance to chemotherapy. This explains the rationale for high dose chemotherapy and radiation, in an attempt to eradicate the stem cell of this lymphoma (this therapy also eliminates the stem cell of the bone marrow). Investigators at Dana-Farber Cancer Institute (Boston, MA) have attempted to accomplish this goal with high-dose cyclophosphamide and total-body irradiation. This therapy ablates the bone marrow and requires support with bone marrow transplantation. The problem with this approach is that the bone marrow is

invariably contaminated with tumor cells. Therefore, the bone marrow was purged of tumor cells *ex vivo*, using a monoclonal antibody cocktail of anti-CD20, CD10 and B5, all with complement. This treatment was performed in patients with advanced stage, but chemotherapy-sensitive disease and resulted in a 5-year disease-free survival in approximately 40% (Freedman, et al, manuscript in preparation). Interestingly, the importance of purging was addressed by Gribben, et al (NEJM 1991;325:1525-1533). In this study, samples of bone marrow before and after purging were assessed for the presence of minimal residual disease by polymerase chain reaction (PCR) for the t(14;18) translocation commonly found in follicular lymphoma. The risk of relapse was 10 times higher in those patients whose bone marrow was positive for disease after purging than those with negative bone marrow. Whether this approach is going to offer a chance for cure in a disease with a long natural history awaits longer follow-up. Interferon- $\alpha$  2b (Intron-A; Schering-Plough) was approved in Canada in September 1995 as an adjuvant treatment for follicular NHL.

**Intermediate-grade NHL** treatment is probably the greatest success in oncology with a 35-50% cure rate with conventional chemotherapy. For patients with localized disease, combination chemotherapy, or abbreviated chemotherapy with radiation therapy, results in cure rates of 80-90%. For patients with advanced disease treated with chemotherapy, 55-60% of patients under 70 are cured, but only 20-30% of those over 70 years-of-age. During the 1970s, one of the first regimens shown to produce these cure rates was combination chemotherapy with CHOP (cyclophosphamide, Adriamycin, vincristine and prednisone).

For nearly the next 20 years more complex regimens were devised in an effort to improve response rates. These so-called second and third generation regimens produced excellent results in single institution studies. Recently, these regimens were compared head-to-head in a multi-institutional study and were found to be no better than CHOP, a regimen with lower toxicity (Fisher, et al, NEJM 1993;328:1002-1006). These other regimens were designed to provide a dose escalation of

chemotherapy over CHOP, but this escalation ranged from only 1.2-to 1.5-fold. Therefore, it was not surprising that this small dose escalation did not result in improved survival. However, in a recently-published pilot trial, the cyclophosphamide in CHOP was escalated 5-fold over standard CHOP by the introduction of hematopoietic growth factors. This regimen was used for patients with increased risk of relapse based on the International Prognostic Index. In this study, nearly 70% of patients were disease free, with a follow-up of 20 months, compared to approximately 40% reported in studies using standard CHOP (Shipp, et al, JCO 1995;13:2916-2923). Adoption of this regimen for patients with high-risk disease awaits further follow-up and completion of additional studies.

For patients who experience relapse of disease after initial chemotherapy, the advent of high-dose chemotherapy, with or without total body irradiation, followed by autoBMT, peripheral blood stem cell (PBSC) or alloBMT, has changed the prognosis from uniformly fatal to potentially curable. However, a subset of patients are candidates for this aggressive therapy. Patients who are most likely to benefit from this procedure are those under age 60, with a good performance status and chemotherapy-sensitive disease. There is a 40-50% cure rate in this group of patients who undergo high-dose therapy and BMT. This approach has been proven to exceed that of standard "salvage", or alternative chemotherapy. The PARMA cooperative group took patients who had relapsed after initial therapy and treated them with DHAP chemotherapy for 2 cycles. Responding patients were then randomized to receive 4 further cycles of DHAP or high-dose therapy and BMT. The results were recently reported in abstract form, showing improved survival in the BMT arm.

**High-grade NHL** is rare in adults. These lymphomas are highly aggressive with a high growth fraction. Therefore, they are treated with high-intensity, brief duration combination chemotherapy regimens. These subtypes have a high propensity to involve the central nervous system. Therefore, a lumbar puncture is required for staging, as well as prophylactic intrathecal chemotherapy.

**Exhibit 8**  
**Estimated Allogeneic and Autologous Transplants for Lymphoma/Multiple Myeloma in Europe (1993)**

Indication			ALLOGENEIC		AUTOLOGOUS			
	Total (#)	Total (%)	BMT (#)	Total (%)	BMT (#)	PBSC alone or with BMT (#)	Total (#)	Total (%)
NHL	1,433	53.7	99	6.9	633	701	1,334	93.1
HD	637	23.9	9	1.4	328	300	628	98.6
Multiple Myeloma	596	22.4	89	14.9	114	393	507	85.1
<b>TOTAL</b>	<b>2,666</b>	<b>100.0</b>	<b>197</b>	<b>7.4</b>	<b>1,075</b>	<b>1,394</b>	<b>2,469</b>	<b>92.6</b>

Source: European Group for Blood and Marrow Transplantation (EBMT)

With aggressive treatment, 40-50% of patients can be cured. Because of the rapid growth of this NHL subtype, patients who do not respond to therapy have a dismal prognosis and are poor candidates for alternative therapies because of poor performance status.

**Multiple Myeloma**

Standard form of therapy for multiple myeloma has remained unchanged for the past 25 years. Oral melphalan (Alkeran; Glaxo Wellcome) and prednisone (MP regimen) result in response rates of 50% to 60%. Because of variable absorption, the dose of melphalan needs to be adjusted to cause a minimal reduction in white blood cell count after 4 weeks of therapy. The response to therapy itself is an important predictor of prognosis. In one study, median survival of patients who responded to therapy, had stable disease, or progressive disease was 48, 49 and 15 months, respectively (Bergsagel, et al, JCO 1988;6:757-758). Prognosis is poor in patients who do not respond to this regimen and are treated with second-line chemotherapy.

Many combinations of chemotherapy have been used in an attempt to improve upon the results of melphalan and prednisone. An examination of 18 trials comparing combination chemotherapy with MP showed no overall difference (Gregory, et al, JCO 1992;10:334-342). However, this study found that in cases of increased median survival with MP, patients did better than those who received combination chemotherapy. This would indicate that patients with a good prognosis fare better with MP and those with more aggressive disease may do better with alternative regimens. Unfortunately, regardless of the chemotherapy used, 30-50% of patients do not respond, those who do respond will eventually relapse, and none are cured.

Patients who have progressive disease after initial therapy have about a 40% response rate to glucocorticosteroid therapy. Alternatively, patients can be treated with second-line chemotherapy using a regimen such as VAD (vincristine, Adriamycin and dexamethasone) which is associated with a high response rate, but of short duration. This is partially attributed to elevated levels of the multi-drug resistance protein, which has been documented in these cells. Attempts to reverse multi-drug resistance using verapamil, tamoxifen or cyclosporine, while administering chemotherapy such as VAD, are in progress.

*Interferon-α* has been found to have some efficacy in multiple myeloma, particularly when the tumor burden is low. In an attempt to improve the duration of response, a recent trial randomized patients who responded to MP

to interferon or no further therapy (Browman, et al, JCO 1995;13:2354-2360). A modest survival benefit was found in those patients who received interferon with median survival of 43 versus 35 months.

*High-dose chemotherapy* and total body irradiation with BMT or PBSC support has been used by several investigators because myeloma cells have been documented to be sensitive to chemotherapy and radiation. This approach, which is usually attempted in younger patients because of its toxicity, is limited by the fact that fewer than 40% of patients have a compatible bone marrow donor. AutoBMT support has also been used, but it is complicated by tumor cells contaminating the marrow. Nevertheless, CR rates reported of 50%-60% and there are relapse-free survivors 15 years post-transplant. However, median response has only been 16-24 months. The largest group of patients to undergo this approach has been reported by the European Group for Blood and Marrow Transplantation (EBMT). The overall survival in this trial was 28% at 7 years. A large study is currently underway to determine whether this approach is better than standard therapy.

There is definitely a trend to use PBSC transplants with/without autoBMT in the management of multiple myeloma earlier in the course of the disease. A benefit was observed in a retrospective analysis of 16 patients administered standard chemotherapy followed either by PBSC transplants (15 patients) or BMT (one patient). With the exception of one toxic death, median survival had not been reached at three years and disease-free survival was 25 months (Abdel-Razeq, et al, Blood, Vol 86, No 10, Supplement to Nov 15, 1995, Abs. 3731).

High-dose melphalan (140 mg/m<sup>2</sup>) as front-line therapy results in high remission rates but causes severe hematologic toxicity. AutoBMT may mitigate such toxicity but introduces an increased risk of re-infusing into the patient potentially contaminated marrow/blood. An alternative method to induce hematopoietic recovery is via the administration of colony stimulating factors (CSF) without the use of autoBMT. Among 117 patients who were previously treated with standard chemotherapy, three (2.5%) died while treated with high-dose melphalan and G-CSF (Lenograstim, Granocyte; Chugai, Rhône Poulenc Rorer), administered subcutaneously at a

Indication	Total (#)	Total (%)	Allogeneic (#)	Total (%)	Autologous* (#)	Total (%)
NHL	3,935	55.9	496	12.6	3,438	87.4
HD	1,567	22.3	50	3.2	1,517	96.8
Multiple Myeloma	1,538	21.8	435	28.3	1,103	71.3
<b>TOTAL</b>	<b>7,040</b>	<b>100.0</b>	<b>981</b>	<b>13.9</b>	<b>6,058</b>	<b>86.1</b>

\* Includes both bone marrow and peripheral blood stem cell transplants

daily dose of 5 µg/kg, and 5 experienced prolonged neutropenia (30 >days). G-CSF reduced the time of neutrophil recovery to 18 days versus 23 days and was well tolerated. However, in terms of remission rates, patient outcome with G-CSF was comparable to controls (Harousseau JL, et al, Blood, Vol 86, No 10, Supplement to Nov 15, 1995, Abs. 725).

**Adjunct therapies** are also added to standard chemotherapy to mitigate some of the more serious complications of multiple myeloma. For instance, epoietin α (erythropoietin, EPO) was clinically evaluated in multiple myeloma-associated anemia in a randomized, double-blind trial involving 25 patients in a stable phase of the disease. Patients were treated with subcutaneous EPO (150 U/kg) thrice weekly for 12 weeks. Hematocrit values rose to 38% or more in 6 of 10 patients who completed the regimen, compared to no increases in the control group (Garton JP, et al, Arch Intern Med 1995 Oct. 23, 155(19):2069-74).

Pamidronate disodium (Aredia; Ciba-Geigy), a bisphosphonate, was approved in September 1995 as a treatment of skeletal osteolytic lesions in multiple myeloma in conjunction with standard chemotherapy. A supplemental NDA for this indication, filed in February 1995, was recommended unanimously by the oncologic drugs advisory committee (ODAC) of the FDA in July 1995. Aredia has been commercially available in the USA for the treatment of hypercalcemia associated with malignancy since 1991 and Paget's disease since 1994. It is marketed in the USA exclusively by Chiron Therapeutics (Emeryville, CA). Two other bisphosphonates, etidronate disodium (Didronel; Procter & Gamble) commercially available in the USA and abroad and clodronate (Bonefos; Leiras and Clasteon; Gentili) sold outside the USA for the treatment of hypercalcemia, do not match the effectiveness of pamidronate which was shown to be 100 times more potent than etidronate and 10 times more potent than clodronate in preventing bone resorption *in vitro*. Oral etidronate was ineffective in preventing skeletal complications in a large double-blind placebo-controlled trial. In a similar trial, oral clodronate added to standard chemotherapy did not lessen bone pain or reduce bone fractures in spite of significantly reducing progression of osteolysis. In contrast, IV pamidronate, administered every four weeks for nine cycles, resulted in prevention of skeletal events and hypercalcemia, reduction of fractures, alleviation of bone pain and increased survival in patients with stage III multiple myeloma (Berenson JR, et al, NEJM, Feb. 22, 1996, 334:488-493).

*Editor's note: Next issue will discuss putative mechanisms involved in hematologic malignancies and present a comprehensive review of new therapies and agents in development for the treatment of such malignancies, including novel chemotherapeutics, monoclonal antibodies, immunoconjugates, gene therapy, vaccines, etc.*

## MEETING COVERAGE

### NEW ADVANCES IN THE TREATMENT OF OVARIAN CANCER

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

#### CHEMOTHERAPY

Chemotherapy for advanced ovarian cancer remains largely suboptimal underscoring the need for new treatment approaches at relapse or in order to prevent relapse. Generally, although response rates with chemotherapy in ovarian carcinoma are high, overall survival remains low.

#### Large-scale Prospective Trials

Chemotherapy for advanced ovarian cancer has constantly evolved over the last 20 years based on the findings of prospective clinical trials. In the 544-patient Intergroup trial a survival advantage was observed with intraperitoneal compared to intravenous cisplatin following optimal debulking surgery. In the EORTC-GCCG trial, which recruited 425 patients with bulky disease at completion of primary surgery, survival was prolonged when interval debulking surgery was performed after three cycles of chemotherapy. Combination chemotherapy with paclitaxel and cisplatin was shown to offer a significant survival advantage in comparison with cisplatin and cyclophosphamide in the GOG trial, which encompassed 410 suboptimally debulked patients with advanced ovarian cancer. These trials clearly have important implications for the future management of ovarian cancer patients in terms of clinical outcomes and economic considerations. For these reasons, the second and third studies currently are being repeated by other groups in order to confirm their findings and preliminary results are expected within the next two years.

#### Anthracyclines

Also, anthracyclines are coming back into favor as potentially useful partners in first-line chemotherapy of ovarian cancer. Several meta-analyses have pointed to a survival advantage linked to their use and they seem to display an impressive synergism with taxoid compounds.

#### Platinum-resistant Disease

In the so-called "salvage" setting, the platinum-free interval concept has gained in popularity and has stimulated operational definitions of platinum resistance and sensitivity. There now are a number of treatment options for platinum-resistant patients including, docetaxel, paclitaxel, etoposide, hexmethyamine, topotecan, oxaliplatin and high dose epidoxorubicin, but none of them is ideal. For this reason, an active search for new drugs in this setting remains a high priority.

Finally, with the expanding knowledge of the biology of ovarian cancer, it is possible to start pointing toward new molecular targets for treatment intervention. These would include transmembrane tyrosine kinase growth factor receptors, matrix metalloproteinases, vascular endothelial growth factor among others (Piccart MJ, Sixth ICAT, Educational Lecture 04).

### Prognostic Factors for Response to Second-Line Treatment

Time from last chemotherapy is a well established predictor of response to second-line treatment in relapsed ovarian cancer. Analysis of a recent European-Canadian trial of paclitaxel (382 patients, 66 responders) and an EORTC-GCCG trial of epirubicin (105 patients, 22 responders) suggest that serous histology, maximum tumor bulk less than five centimeters and normal hemoglobin might also favorably affect response. Subsequent analyses on data sets from similar trials of irinotecan (55 patients, 13 responders), gemcitabine (153 patients, 21 responders), docetaxel (135 patients, 35 responders), and carboplatin (273 patients, 32 responders) have been analyzed, with the overall six trials encompassing a total number of 1,103 patients. An overview analysis of all six studies concluded that all four factors have an important effect on response rate. It is, therefore, important to describe these tumor and patient factors when reporting results of therapy in platinum-pretreated ovarian cancer patients (Vermorken JB, et al, Sixth ICAT, Abs. #355, Pg 130).

### Monotherapy

Paclitaxel (Taxol; Bristol-Myers Squibb) as a three-hour infusion showed good activity in platinum-pretreated ovarian cancer patients. Survival improved significantly in women with good performance status (ECOG:0) and only one previous chemotherapeutic regimen, with no difference between platinum-resistant or platinum-sensitive individuals.

In a prospective phase II study, 51 women with advanced ovarian cancer who progressed or relapsed after platinum chemotherapy were given paclitaxel (175 mg/m<sup>2</sup>) as a three-hour infusion every three weeks. Only patients with a maximum of two previous chemotherapeutic regimens were included. Thirty-nine of these women were treated with one prior chemotherapeutic regimen, while 12 were subjected to two regimens. Median time from prior treatment was four months.

In 47 evaluable patients, there was an overall objective response rate of 28%, with eight CRs (17%) and five PRs (11%). Ten persons (21%) demonstrated stable disease. The CRs were all in women pretreated with only one prior chemotherapeutic regimen. The median survival was 16 months and the time to progression was 11 months (Aravantinos G, et al, Sixth ICAT, Abs #698, Pg 228).

### Combination Chemotherapy

Irinotecan (Campto; Rhône-Poulenc Rorer), a new topoisomerase I inhibitor, in combination with mitomycin C (Mutamycin; Bristol-Myers Squibb) was shown to be highly effective for advanced clear-cell adenocarcinoma of the ovary, an advanced ovarian malignancy which generally has a much worse prognosis compared with the more common serous cystadenocarcinoma. Based on earlier *in vitro* and animal studies, a combination was designed including irinotecan (120 mg/m<sup>2</sup> in 500 ml of saline) as a four-hour infusion on days one, 15, and 29 and mitomycin C (7.0 mg/m<sup>2</sup>) as a bolus injection also on days one, 15, and 29. The course was repeated at three-week intervals.

Twenty evaluable patients received an average of 2.5 courses of treatment each, with an overall objective response rate of 60% (12/20). This included eight CRs, four PRs, and disease stabilized in eight women. Of special importance was the fact that the 12 responders survived significantly longer compared to the eight non-responders, with a median survival after entry of 20 months versus six months (Shimizu Y, et al, Sixth ICAT, Abs. 354, Pg 130).

Paclitaxel and carboplatin (Paraplatin; Bristol-Myers Squibb) proved to be effective in patients with pretreated advanced ovarian cancer. In addition, this regimen is attractive because it can be administered on an outpatient basis. Overall, 73 patients with measurable advanced ovarian cancer and no more than two lines of chemotherapy without taxanes (at least one platinum-based regimen) received paclitaxel (175 mg/m<sup>2</sup>) in a three-hour infusion followed by carboplatin (AUC 5 mg per ml per min) over 30 minutes, every three weeks. AUC was calculated by Calvert formula. The overall objective response rate in 64 evaluable patients was 41%, with eight CRs (12%) and 18 PRs (29%). Median duration of response was eight months. Patients did better if their best response at the last platinum-based regimen was complete or if their interval from their last platinum-based regimen was greater than 12 months (Orfeuvre C, et al, Sixth ICAT, Abs. #353, Pg 130).

A combination of carboplatin, cisplatin (Platinol; Bristol-Myers Squibb) and ifosfamide (Ifex; Bristol-Myers Squibb), although relatively toxic hematologically, has been shown to be highly active against advanced ovarian cancer. Thirty-eight women with advanced ovarian cancer were entered in a phase I/II dose-ranging clinical study, to determine the maximum tolerated dose of cisplatin administered in combination with carboplatin (300 mg/m<sup>2</sup>) on day one and ifosfamide (4000 mg/m<sup>2</sup>) beginning on day one. The initial dose of cisplatin was 40 mg/m<sup>2</sup> on day eight, escalated by 10 mg/m<sup>2</sup> up to the maximum tolerated dose (MTD). Based on patient tolerance cisplatin was administered at 40 mg/m<sup>2</sup> in four women, 50 mg/m<sup>2</sup> in six, 60 mg/m<sup>2</sup> in 22, 70 mg/m<sup>2</sup> in six. Patients averaged five cycles of chemotherapy, with 187

cycles being administered overall. In more than a third of the cycles, drug administration was delayed because of hematologic recovery failure. Grade 3/4 leukopenia and thrombocytopenia were observed in 54% and 49% of the treated women, respectively, but toxicity was never life threatening. Overall objective response rate for all 38 patients was 92% (35/38) with 19 CRs and 16 PRs. MTD was reached at 70 mg/m<sup>2</sup> (four of six treated patients demonstrated grade 4 thrombocytopenia). The dose recommended for the phase II study, therefore, is 60 mg/m<sup>2</sup> (Leone B, et al, Sixth ICAT, Abs. #349, Pg 129).

An accelerated combination of cisplatin, epidoxorubicin, and cyclophosphamide (Cytosan; Bristol-Myers Squibb) appears feasible for patients with advanced ovarian cancer. Because dose intensity of chemotherapy may be important for clinical outcome in ovarian cancer, the feasibility of a 100% increase in dose intensity of the cisplatin, epidoxorubicin, and cyclophosphamide combination was evaluated by reducing intervals between cycles. Twenty-two women with advanced ovarian cancer who entered into the trial were administered IV cisplatin (50 mg/m<sup>2</sup>), epidoxorubicin (60 mg/m<sup>2</sup>) and cyclophosphamide (600 mg/m<sup>2</sup>) on day one every 14 days for six cycles. Granulocyte-colony stimulating factor (G-CSF) (Neupogen; Amgen) was also administered subcutaneously from day four to day nine between cycles. Twenty-one of the patients who remained in the study were administered six cycles of the combination regimen without any dose reduction. Of these, 19 women were treated by at least 85% of the planned dose intensity and 13 by 100%. Non-life-threatening toxicity was observed and marrow toxicity was comparable to that seen during conventional treatments. Also, no severe mucositis or thrombocytopenia was reported (Pronzato P, et al, Sixth ICAT, Abs. #346, Pg 128).

### Aortic Infusional Chemotherapy

Although it has not provided any real survival benefits, aortic infusional chemotherapy offers patients with advanced, progressive ovarian cancer, a substantially improved quality of life. Forty-five women with progressive, advanced (stage IIIc or IV) ovarian cancer, who did not respond to prior systemic chemotherapy, underwent regional chemotherapy administered via a thigh aortic catheter in cycles one and two and as an aortic stop-flow infusion in cycle three. The drugs administered were doxorubicin (50 mg), mitomycin C (14-20 mg), and cisplatin (2 x 50 mg), with an upper thigh block in the first two courses, and mitomycin C (20 mg) plus doxorubicin (50 mg) in stop-flow infusion.

Overall clinical response rate was 93% (42/45), with five CRs (11%), 21 PRs (47%), and 16 MRs (33%). Complete resolution of ascites occurred in nine of 33 women, with a reduction of more than 50% in 14 other patients. In addition, performance improved in 60% (27/45) of the women and remained stable and unchanged in 20% (9/45). Median survival was 12.5 months and median

time to progression was 8.6 months. Side effects were mild and severe bone marrow depression was not observed (Gailhofer S and Aigner KR, Sixth ICAT, Abs. #352, Pg 130).

### RADIATION THERAPY

Radiation therapy, when administered in conjunction with surgery and chemotherapy was shown to significantly extend overall survival in patients with ovarian cancer. In a retrospective study, 60 patients with various stages of ovarian cancers (8 in stage I, 9 in stage II, 39 in stage III, and 4 in stage IV) were successfully treated between 1976 and 1983. Serous cystic adenocarcinoma was present in 55 women (92%). Radiation therapy included the abdomen and pelvis in 38 patients and the pelvis alone in 22 patients. Overall survival at five and 10 years was 33.8% and 28.9%, respectively.

Despite the fact that radiation therapy has demonstrated some efficacy, it is rarely, if ever, used in ovarian cancer patients. However, positive retrospective findings suggest that radiation therapy should play a role in the management of ovarian carcinoma (Benmiloud M, et al, Sixth ICAT, Abs. #701, Pg 229).

### IMMUNOTHERAPY

#### Biomira

Sialyl TN-KHL (STn-KHL) immunotherapy has demonstrated activity as a therapeutic vaccine in advanced ovarian cancer. Because increased expression of the disaccharide tumor epitope sialyl-Tn is associated with a poor prognosis in several cancer types, including ovarian cancer, an evaluation of the safety and efficacy of an immunotherapeutic vaccine (Theratope; Biomira) composed of STn-KHL with Detox B adjuvant was carried out at the Cross Cancer Institute (Edmonton, Canada) in patients with evaluable disease after conventional therapy for advanced ovarian cancer. Thirty-six women were initially given IV cyclophosphamide (300 mg/m<sup>2</sup>) three days prior to the first vaccination. Patients were administered Theratope vaccine at 0, 2, 5, and 9 weeks, followed by four more monthly injections. Therapy was discontinued when disease progression was observed.

Six women were taken off the study (one withdrew, one experienced an adverse reaction, and disease progressed in four). Of 26 evaluable patients, two experienced a PR and 10 had stable disease at 12 weeks with four of these patients exhibiting stable disease after 29 weeks and two after 22 and 20 months. Generally, patient acceptance was excellent. The vaccine proved to be a potent inducer of IgG and IgM antibodies against STn and KLH. Median time to disease progression was 3.1 months for the entire group. The partial responses suggest vaccine activity in advanced ovarian cancer, making STn-KLH immunotherapy a candidate for further study for use in consolidation therapy (Ehlen T, et al, Sixth ICAT, Abs. #350, Pg 129).

## TECHNOLOGY & MARKET UPDATE

### APPLICATIONS OF CONTRAST MEDIA IN CANCER IMAGING

- Contrast media are used to enhance the diagnostic capability of various imaging modalities, such as x-ray/computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound
- The overall USA market for contrast media is estimated at \$1,392 million in 1995 and is forecast to reach \$1,934 million in 1999. The radiology portion (excluding cardiology) is estimated at \$927 million in 1995 and forecast to reach \$1,142 million in 1999 (see Exhibit 10)
- Information presented here is based on Report # 201 entitled, *The U. S. Market for Medical Imaging Contrast Media-Technologies, Products, Clinical Applications, Markets and Competitive Analysis*, prepared by Bio-Tech Systems and published by NEW MEDICINE

### BACKGROUND ON CONTRAST MEDIA

The key medical diagnostic imaging modalities are x-ray/computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound. Another major imaging modality, nuclear medicine, that uses radioisotopes to image internal tissues and organs, also competes in this sector. Contrast agents are currently available for all major diagnostic modalities and are being increasingly used for an ever-expanding number of indications. Improvement in image quality by the use of contrast media not only increases the utility of a particular imaging modality for a given indication, but also broadens its applicability to other, sometimes more lucrative, indications. Therefore, improved imaging capability may serve as a means for a modality to increase its market share, benefiting both hardware and consumables suppliers.

In addition to image enhancement, contrast media may serve as drug delivery and therapeutic agents, further expanding their market opportunity. In drug delivery applications, formulations of contrast agents have successfully delivered chemotherapeutics to tumor cells and transported and delivered oxygen to tissues. In therapeutic applications such agents have been evaluated as radiosensitizers to enhance the effects of radiation on tumors and photosensitizers to improve the effectiveness of photodynamic therapy in cancer. Ultrasound contrast agents, such as albumin-stabilized microbubbles, may also be used to enhance tumor-killing attributes of certain cytotoxic substances that cannot be used alone in adequate concentrations because of excessive toxicity. Cancer therapy using acoustic cavitation is supported by the hypothesis that cell damage is caused by a sonochemical rather than to a sonomechanical process (Jeffers

RJ, et al, *Journal of the Acoustical Society of America*, 1995 Jan, 97(1):669-76). Ultrasound contrast agents may also be used as alternative therapeutic drug enhancers for thrombolysis (Tachibana K and Tachibana S, *Circulation*, 1995 Sep 1, 92(5):1148-50).

The original contrast media were low-cost iodinated ionic compounds used to enhance x-ray imaging. The advent of iodinated nonionic compounds with their improved safety profile, boosted the worldwide market for such agents to over \$2 billion in 1995. Currently, although iodinated nonionic contrast media dominate the worldwide market, their growth outlook is limited as they represent a mature segment.

### CONTRAST MEDIA-ENHANCED IMAGING MODALITIES IN TUMOR IMAGING

Contrast-enhanced imaging is particularly attractive in the detection and monitoring of cancer.

#### Radiography

**Fluoroscopy**, using orally ingested barium sulfate, is used to identify lesions of the stomach, small and large intestine and colon. Fluoroscopy, using injectable contrast media, is also used to visualize the vasculature to guide catheters to embolize blood vessels nourishing tumors.

**Angiography**, enhanced mostly (85%) by nonionic iodinated media, is used in both vascular and non-vascular procedures to visualize such organs as the liver, kidney and gallbladder, among others.

#### Computed Tomography (CT)

CT images incorporate more information on soft tissue pathology than simple radiography. Enhanced CT took off with the introduction of nonionic agents in late 1985. Currently, approximately 50% of all CT studies use either iodinated ionic (38%) or nonionic (62%) contrast media. CT is widely used in tumor imaging.

#### Magnetic Resonance (MRI)

MRI has proven a very versatile imaging modality with far reaching applications. It also represents one of the most attractive near-term market for contrast agents. MRI is routinely employed in the developed world. It is believed that, currently, nearly all healthcare facilities in the developed countries that can justify ownership of an MRI unit, have installed one, and units are being installed at a fast pace in the third world. Lower-cost and used/refurbished MRI systems are contributing to the expanding equipment base worldwide. There is, therefore, a unique resource in place to be tapped by manufacturers of contrast media. In turn, expanded applications of MRI, that may result from the availability of contrast media, serve to justify hardware installation by increasing utilization, improving productivity and favorably impacting the economics of operating these very costly devices.

Contrast-enhanced MRI is a relatively new development, first introduced in the USA in 1988 with the launch of Magnevist by Berlex. In the interim, two additional agents entered the market, Bracco's ProHance and Nycomed's Omniscan. Currently, approximately 30% of MRI procedures use contrast media. All injectable MRI contrast agents on the market today consist of gadolinium, a paramagnetic material, tightly bound to DTPA (or other appropriate ligands) which virtually surrounds gadolinium, a very toxic substance, and prevents it from interacting with the host. Gadolinium-DTPA agents are very versatile. They remain in a soluble form at high concentrations, circulate as liquids rather than colloids or suspensions and consist of small enough molecules to be readily cleared by the kidneys. Berlex holds the patents for gadolinium-based MRI contrast agents and receives royalties from Bracco and Nycomed.

Alternative materials evaluated as MRI contrast media include manganese compounds in development as oral bowel markers and ferrites (iron oxides) that are suitable for organ-specific applications such as liver imaging. Other tissue-specific agents include microaggregated albumin for lung imaging, pyrophosphates for heart imaging, lipid solutions such as iodoamphetamines that cross the blood brain barrier, and various perfusion agents that mimic naturally-occurring substances.

Contrast-enhanced MRI, that highlights equivocal tissue boundaries, is becoming a very important diagnostic tool in the detection and management of cancer. MRI imaging is uniquely suited in detecting brain tumors and, particularly, pituitary tumors. It also can verify the three-dimensional structure of a lesion by imaging multiple planes along the three perpendicular axes of the body, without moving the patient. Other malignancies better imaged by enhanced MRI than CT, include head and neck, pancreatic, kidney and liver cancers. Enhanced MRI is being increasingly deployed in the staging and evaluation of breast cancer (see FO, V1, #9, p 216). Staging of prostate cancer has also been carried out using enhanced MRI to distinguish localized prostatic tumors from those that have spread beyond the capsule. Enhanced MRI is also a sensitive and specific imaging modality in assessing tumor response to treatment (chemotherapy and/or radiotherapy) because rapidly growing tumors absorb greater amounts of contrast.

**Exhibit 10**  
**Estimated and Forecast Contrast Media Markets in Radiology in the USA (1995 & 1999)**

Contrast Agent	1995E	1999F	CAGR (%)
Iodinated Nonionic & Low Osmolar	663.8	707.4	1.60
CT	535.5	588.2	2.37
Other Non-Vascular	128.3	119.2	-1.82
Iodinated Ionic	49.3	58.1	4.19
CT	26.2	32.7	5.70
Other Non-Vascular	23.1	25.4	2.40
MRI	158.6	240.9	11.02
Ultrasound		66.4	
Barium Sulfate	55.6	68.8	5.47
<b>TOTAL</b>	<b>927.3</b>	<b>1141.6</b>	<b>5.34</b>

Note: excludes contrast media markets for cardiology applications

Source: New Medicine report #201, The U. S. Market for Medical Imaging Contrast Media-Technologies, Products, Clinical Applications, Markets and Competitive Analysis, August 1995.

Liver studies are the prime targets of developers of tissue-specific MRI contrast agents. Superparamagnetic iron oxide-based contrast agents are uniquely suited in the detection of primary and metastatic liver cancer.

Enhanced MRI may be potentially deployed in virtually all tumor imaging indications. This promising outlook has spawned numerous programs that are pursuing development of both injectable and oral MRI contrast agents. Injectable agents in development are organ-specific, whereas oral agents are used as bowel markers to aid in delineating tissues of interest in the abdomen. Availability of such agents is expected to broaden the application of MRI, possibly at the expense of other modalities.

### Ultrasound

Ultrasound imaging with its high volume and the ubiquitous presence of relatively low-cost hardware, has been an attractive target for developers of contrast media. To date, most of the emphasis in the development of contrast media in ultrasound has focused on cardiology applications. However, intense R&D efforts are underway to develop ultrasound contrast media for a variety of imaging applications, including cancer.

Because, there is a wider availability of echogenic (ultrasound reflective) than photoelectric or magnetic compounds, developers of ultrasound contrast media are in a unique position to create novel patentable entities with a promising market outlook.

Injectable echogenic contrast media must be biocompatible and biodegradable. Most agents under development consist of microscopic gas bubbles (about 5 microns in diameter) suspended in a carrier or enclosed in lipid or polymer coatings. There is a trade-off in the selection of coatings; lipid or liposomal coatings are safer but less rugged than polymer coatings.

## COMPETITIVE STRUCTURE OF THE INDUSTRY

The leading supplier of contrast media in the USA is Nycomed, controlling approximately 40% of the overall market and 45% of the iodinated nonionic radiology contrast media segment. Bracco Diagnostics and Mallinckrodt Medical hold the second and third largest market share in this segment. The leading supplier of MRI contrast media is Berlex with a 65% market share, followed by Nycomed and Bracco. E-Z-EM is the major supplier of barium sulfate contrast media controlling nearly 85% of the market. Lafayette Pharmaceutical (Fort Worth, TX), divested by E-Z-EM in 1991, is a distant second. The ultrasound contrast media segment was ushered in 1994, with the commercialization of Albunex, developed by Molecular Biosystems for cardiology applications. Ultrasound contrast media for tumor imaging are still in the developmental stage.

Generally, sales of contrast media in the USA have been experiencing increased pressure from discounting, spurred by competition and end-user cost-cutting trends. Also, patents of several major brands of contrast media will be expiring in the next few years, creating an opportunity for generic versions that will result in further price erosion. The intense development activity in this sector reflects the opportunity for novel agents with unique features that can be priced at considerably higher levels.

Average prices of contrast media at the manufacturer's level are estimated at \$5.5 per dose for barium sulfate, \$8 for iodinated ionic agents, \$67 for MRI media, \$85 for ultrasound agents, and \$93 for nonionic agents. Generally, contrast media used in cardiology are more expensive than those used in radiology. Newer agents with more attractive imaging capabilities, are expected to command higher prices but, generally, across the board cost-containment efforts will hold prices in check in this sector.

Contrast media represent a growing worldwide market. Among suppliers of contrast media outside the USA are Daiichi Pharmaceutical (Tokyo, Japan), a licensee of several Nycomed contrast media in Japan, and Guerbet, a supplier of its own and licensed contrast media in Europe.

## UPDATE ON MAJOR SUPPLIERS/DEVELOPERS OF CONTRAST MEDIA

### Acusphere

Acusphere (Cambridge, MA) is developing contrast media for ultrasound, x-ray, CT and MRI using its synthetic polymer and microencapsulation technologies. Its leading product is intended for myocardial perfusion studies.

### Advanced Magnetics

Advanced Magnetics (Cambridge, MA), a public company, is developing MRI contrast agents based on its paramagnetic and superparamagnetic colloids. Products under development include :

- Combidex (previously known as AMI-227, an ultrasmall iron oxide particle MRI contrast agent to image lymph nodes, and the liver and spleen, to detect metastatic disease, has entered phase III clinical trials in the USA; licensed to Guerbet for Western Europe and Brazil and to Eiken Chemical (Tokyo, Japan) in Japan
- Feridex I.V., an injectable MRI contrast agent for the detection of primary and metastatic lesions in the liver and spleen; an NDA for this agent was filed in February 1994 and the company received an approvable letter from the FDA in February 1996; it is licensed exclusively to Berlex Laboratories in the USA and Canada under an agreement entered in February 1995 (Berlex paid a \$5 million non-refundable fee on signature and will pay an additional \$5 million fee when the agent is approved by the FDA); in Europe, where it was approved in September 1994, it is marketed by Guerbet (Aulnay-sous-Bois, France) as Endorem; it is licensed in Japan to Eiken Chemical
- GastroMARK (ferumoxil), an oral MRI contrast agent for marking the bowel in abdominal diagnostic imaging; an NDA was filed in January 1994; it is licensed to Mallinckrodt in the USA, Canada and Mexico and it is being sold in Western Europe by Guerbet as Lumirem
- AMI-HS, a hepatocyte-specific second generation MRI agent that uses arabinogalactan as a drug delivery vehicle to the liver; an IND was filed in December 1994 and phase I trials have been completed; licensed to Guerbet in Western Europe and Brazil

In May 1995, Advanced Magnetics entered into a research and licensing agreement with Massachusetts General Hospital (Boston, MA) covering organ-specific, receptor-directed ultrasmall superparamagnetic iron oxide particles for use as MRI contrast agents. Initially the collaboration will target the pancreas.

### Alliance Pharmaceuticals

Alliance Pharmaceuticals (San Diego, CA), a public company, is developing pharmaceuticals based on perfluorochemical (PFC) and emulsion technologies. Imagent US, a PFC-based IV contrast agent for ultrasound imaging, is in preclinical. An oral MRI contrast agent, Imagent GI (perflunon), that was approved by the FDA in August 1993, did not succeed in capturing a significant share of the market, probably because of its high cost, and was virtually abandoned.

### Berlex Laboratories

Berlex Imaging, a division of Berlex Laboratories (Wayne, NJ), which is a subsidiary of Schering AG (Berlin, Germany), dominates the USA MRI market segment. Products on the market include:

- Magnevist (gadolinium-DTPA), for MRI applications, is the leading MRI contrast agent worldwide with sales of about \$270 million; used primarily for central nervous system imaging
- Ultravist (iopromide), an iodinated nonionic agent for x-ray/CT applications sold worldwide, was approved by the FDA in May 1995 and launched in the USA in July 1995 for several intra-arterial and intravenous applications; as part of the approval agreement Berlex will further evaluate Ultravist in three phase IV clinical trials
- Echovist, a saccharide-based ultrasound contrast agent, for cardiologic and gynecologic applications

Contrast agents under development include:

- Levovist, also a saccharide-based ultrasound contrast agent, in phase III trials for cardiologic imaging
- Resovist, an organ-specific MRI agent for liver and spleen imaging, in phase III trials worldwide
- Eovist-DTPA, a gadolinium-based MRI agent for liver imaging, in phase II clinical trials
- Cavisomes, an injectable ultrasound contrast agent in early stages of development that consists of bubbles, less than 3 microns in diameter, coated with cyanoacrylate, a biocompatible and biodegradable medium that extends the life of the agent; targeted for liver imaging; the microbubbles, injected intravenously, travel to the liver, are taken up by reticuloendothelial cells in normal tissue and then rupture at certain Doppler frequencies giving off a color signal that differentiates normal liver from tumor which does not take up the contrast agent

### Bracco

Bracco Diagnostics (Plainsboro, NJ), a subsidiary of Bracco (Milan, Italy), anchored in the second position in the overall USA contrast media market, was created by the acquisition in mid-1994 of Squibb Diagnostics, and the addition of several products from its European operations. Merck KGaA owns 50% of Bracco. Products on the market include:

- Isovue for x-ray/CT imaging; patent expires in November 1997 after it was extended by 22 months as a result of the GATT agreement
- ProHance, a gadolinium-based contrast agent for MRI applications

Products under development include:

- SonoRx, an oral simethicone-coated cellulose ultrasound contrast agent in phase III clinical trials; licensed from ImaRx
- LumenHance (manganese chloride), an oral biphasic (T1- and T2-weighted) MRI agent for GI and

abdominal imaging, in phase III clinical trials; licensed from ImaRx

- Gadobenate, a gadolinium-based oral MRI agent, extensively tested in clinical trials in Europe
- Iomeprol, an iodinated contrast agent that has been clinically evaluated abroad
- BR-1, an ultrasound contrast agent using sulfur hexafluoride gas enclosed in a phospholipid-coated bubble, developed by Synthetica (Geneva, Switzerland) which was acquired by Bracco; in phase II trials

### Cav-Con

Cav-Con (Cavitation-Control Technology; Farmington, CT), a private company founded in 1979, primarily focuses on microsphere-based ultrasound contrast agents (Filmix) for tumor imaging. The company is developing lipid coated microbubbles (LCM) that exhibit a natural affinity for newly-formed tumors. Because they mimic naturally occurring substances in the body, such as high-density and low-density proteins produced by the liver, they remain in the circulation for extended periods of time. They also appear to traverse tumor cell membranes and are taken up in sufficient accumulation for imaging. This imaging technology was licensed to Israel Chemicals (Ramat Gen, Israel). Filmix has been tested in animals and clinical trials are being planned. LCM may also be used to deliver chemotherapeutics, such as Taxol, to tumor cells.

### Cook

Cook Imaging, a subsidiary of Cook (Bloomington, IN), part of the Cook Group, established in 1982, has concentrated in the development of non-ionic X-ray contrast media. The company received FDA approval in December 1995 for Oxilan (ioxilan) for x-ray/CT imaging applications.

### E-Z-EM

E-Z-EM (Westbury, NY) dominates the barium sulfate market segment. E-Z-EM has also entered into licensing, distribution and marketing agreements with Interactive Medical Technologies and Pharmacies.

### Hafslund Nycomed

Nycomed Imaging (New York, NY), a subsidiary of Hafslund Nycomed (Oslo, Norway), combines the diagnostic imaging business of Sterling Winthrop which was divested by Sanofi after it purchased the pharmaceutical operations of Eastman Kodak, with Nycomed's off-shore operations in this area. Products on the market include:

- Omnipaque (iohexol), the leading nonionic contrast agent with worldwide sales estimated at \$1,000 million
- ImaGopaque (iopentol), marketed off-shore

- Omniscan (gadodiamide), a gadolinium-based MRI contrast agent marketed worldwide; sales were estimated to have grown at a rate of 50% in 1995; a higher-dose formulation is under investigation for the detection of smaller lesions (e.g. in the brain)
- Visipaque (iodixanol; formerly known as Acupaque), a third generation nonionic contrast agent launched in Europe in 1995; this agent was considered approvable by the FDA in late 1995

Products in development include:

- CPT, an organ-specific non-ionic x-ray contrast agent for imaging the liver; an IND to begin clinical trials with this agent has been filed in Sweden
- NanoLymph, a lymph node CT imaging contrast agent in phase I clinical trials in Europe
- NanoBarium, an x-ray imaging contrast agent for GI applications in preclinical
- NUS (New Ultrasound), an ultrasound imaging agent in preclinical
- Mangafodipir/S-095, an organ specific MRI contrast agent to image the liver; an NDA for this agent was filed in October 1995
- Abdoscan, an abdominal MRI contrast agent, in phase III clinical trials

### ImaRx

ImaRx (Tucson, AZ), a private company founded in 1991, is developing contrast agents for several imaging modalities. Among products in development are:

- SonoRx, a GI ultrasound contrast medium is intended for the detection of abdominal conditions such as pancreatic cancer; Bracco, the licensee of this product, has completed clinical trials
- Aerosomes, vascular ultrasound contrast agents for several applications, including tumor imaging and as gene delivery vehicles; MRX-115, in phase II clinical trials, for myocardial perfusion studies; studies with this agent in oncology are being planned; it is licensed to DuPont Merck Pharmaceuticals (Wilmington, DE) for cardiology (in North America, Latin America and Europe) and radiology (except in Europe) applications; DuPont Merck will assume clinical development after ImaRx completes phase II clinical trials
- LumenHance, a GI MRI agent designed to produce positive contrast on T1-weighted images and negative contrast on T2-weighted images, for cancer diagnosis; licensed to Bracco that has filed an NDA
- Menosomes, injectable MRI agent for liver imaging
- MRI contrast agents for lymphatic imaging in pre-clinical development

- TomoRx, an oral negative-contrast GI imaging agent for CT and MRI consisting of gas-filled microspheres

### Interactive Medical Technologies

Interactive Medical Technologies (IMT; Los Angeles, CA), is a public company developing microsphere formulations for medical imaging. These formulations are albumin microspheres filled with iodinated contrast material (accounting for 75% of the weight) which can be used as radiopaque media for CT or echogenic media for ultrasound. These contrast media are being developed for the detection of pulmonary embolism and myocardial ischemia. In January 1996, IMT entered into a broad-based long-term licensing, marketing and distribution agreement with E-Z-EM covering its patented microsphere technology. Under the terms of the agreement E-Z-EM will fund preclinical and clinical trials and has the option to globally market and distribute the resulting agents to be manufactured by IMT.

### The Liposome Company

The Liposome Company (Princeton, NJ) had entered an agreement with Schering AG to co-develop a liposomal nonionic contrast agent (TLC 1-6) in July 1994, but the collaboration was discontinued in March 1995. TLC 1-6, a nonionic agent encapsulated in liposomes is intended as a CT contrast medium for the imaging of tumor metastasis.

### Mallinckrodt Medical

Mallinckrodt Medical (St. Louis, MO) is one of the leading suppliers of x-ray contrast media. Commercial products include:

- Optiray, a nonionic/low osmolar contrast agent for CT; patent expiration has been extended to April 2004 by GATT
- Hexabrix, a nonionic/low osmolar contrast agent for CT; patent extended to May 1997 by GATT
- Alunex, an ultrasound contrast agent licensed from Molecular Biosystems

In October 1995 Mallinckrodt amended its agreement with Molecular Biosystems (MBI), signed in 1998, to include distribution rights of Alunex in all markets not served by MBI's other licensees. As part of the agreement Mallinckrodt acquired MBI common stock worth \$13 million, increasing its stake in the company to 10%. Included in this expanded agreement is FS-069, MBI's new second generation ultrasound agent in clinical trials. Mallinckrodt has agreed to pay \$20 million to fund development of this agent over a 4-year period; additional funding to support clinical development and milestone payments could amount to another \$14.5 million. This agreement extends Mallinckrodt's licensing rights to Alunex and FS069 to either July 2003 or three years

after FS069 gains FDA approval for a cardiology indication, whichever is longest.

Mallinckrodt has also licensed GastroMARK, under development by Advanced Magnetics.

### Metasyn

Metasyn (Cambridge, MA), founded in 1992, is developing MRI contrast agents based on a proprietary technology, receptor-induced magnetic enhancement (RIME), a method to direct MRI agents to tissues and create an enhanced magnetic effect. Products in development include:

- MS-264, a gadolinium-based MRI liver agent in preclinical studies; licensed to Nippon Shoji (Osaka, Japan)
- MS-323, a gadolinium-based MRI blood pool imaging agent in preclinical
- Gadolinium-based tumor-enhancing MRI contrast agents, in collaboration with Massachusetts General Hospital (Boston, MA)

### Molecular Biosystems

Molecular Biosystems (San Diego, CA), a public company, concentrates on the development of ultrasound contrast agents. Alunex was approved in the USA in August 1994 for cardiology applications. It is distributed by Shionogi (Osaka, Japan) in Japan, Mallinckrodt Medical in the USA and all other markets not covered by other licensees. In late 1995, Nycomed, MBI's licensee for the European market, returned all rights to Alunex to MBI in exchange of cash and other considerations. Among products in development are:

- FS069, an organ perfusion agent using albumin-coated bubbles (similar to Alunex) containing fluoropropane gas, rather than air; completed phase I clinical trials as of late 1995; also licensed to Mallinckrodt Medical in most world regions not covered by other licensees; both Shionogi and Nycomed also had rights to FS069 but Nycomed returned all rights to MBI
- Oralex, an oral ultrasound agent for abdominal imaging; completed phase I clinical trials
- Superparamagnetic MRI contrast agents (development was curtailed in 1995 to concentrate on ultrasound contrast agents)

### Pharmacyclics

Pharmacyclics (Sunnyvale, CA), a private company, is developing MRI contrast agents based on its expertise in biometallic chemistry and expanded porphyrins (texaphyrins). In addition to applying its texaphyrin technology to contrast media, the company is developing radiosensitizers (Gd-Tex), in phase Ib/II trials, and photosensitizers (Lu-Tex), in phase I trials, for the treatment of

cancer. Products under development for imaging applications include:

- Gadolite, an oral gadolinium zeolite suspension for MRI imaging of the abdomen and pelvis; phase III trials have been completed and an NDA was filed in September 1995; the product will be manufactured Glaxo Wellcome under an agreement concluded in March 1995; Gadolite will be marketed in North America by E-Z-EM that paid a licensing fee upon signing the agreement in August 1995 and also agreed to additional payments upon completion of certain regulatory and commercial milestones and to share profits on net sales
- Gd-Tex (gadolinium texaphyrin), a radiosensitizer that may also prove useful as an injectable MRI agent to image tumors and atherosclerotic cardiovascular disease

### Sonus Pharmaceuticals

Sonus Pharmaceuticals (Bothell, WA), founded in 1991, became public in October 1995 with an offering of 2.5 million shares at \$7 per share. The company is developing ultrasound imaging agents using a fluorocarbon gas (dodecafluoropentane or DDFP). Microscopic liquid droplets of DDFP are converted to gas microbubbles during administration by the company's proprietary Phase-Shift technology. EchoGen Emulsion, an ultrasound imaging agent exploiting this PhaseShift technology, is being developed for both radiology and cardiology applications. EchoGen is a stable liquid emulsion with several unique features, such as small bubble size which allows it to pass through capillaries in the lungs and other organs; a long half life allowing for sufficient imaging time; and sufficient echogenicity for quality imaging.

EchoGen is currently being evaluated in phase III clinical trials in hepatic, renal, peripheral vascular and cardiac imaging. A pivotal 240-patient phase III clinical trial of EchoGen was initiated in the USA in June 1995 to evaluate the agent's enhancement and visualization capabilities in radiology indications such as liver, kidney and peripheral vasculature imaging. A European phase III trial that is evaluating the agent's performance in imaging studies of the breast, central nervous system, liver, kidney and peripheral vasculature, is also in progress.

In July 1994 Sonus optioned licensing rights to EchoGen for the Pacific Rim to Daiichi Pharmaceutical (Tokyo, Japan) that later exercised the option agreeing to a commitment of \$33 million, with \$7 million paid up-front and the remaining \$25 million payable upon achievement of certain milestones. As a result of the agreement Daiichi owns 4% of Sonus. Guerbet also paid Sonus \$4.7 million to acquire an option to market EchoGen in Europe. Part of this fee is to be converted to Sonus stock. Also, under a supply agreement, Abbott Laboratories (Abbott Park, IL) will provide Sonus with EchoGen in final, packaged form.

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